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On the Relative Importance of Genetic and Environmental Factors in the Determination of Human Hair Pigment Concentration[1]

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INTRODUCTION

FROM THEIR EARLY STUDY of the inheritance of human hair color Davenport and Davenport (1909) concluded that all hair colors are the result primarily of different relative concentrations of brown and reddish pigments in the hair, and that the presence of red pigment, and its concentration, are genetically independent of the presence of brown pigment or of its concentration. The concentrations and chemical constitutions of the pigments are, however, dependent upon the activity of living precursor pigment cells (melanoblasts) in the epidermis, and this activity is not constant under all environmental conditions. The production of pigments is affected by nutritional factors (Frost, 1948), by light (Bissonette and Bailey, 1944) and temperature (Iljin, 1931; Danneel, 1937) and by endocrine secretions (Forbes, 1942; Spoor and Ralli, 1944; Dieke, 1947; Hamilton, 1948). Thus the concentrations of pigments produced by the melanoblasts may be partially the result of environmental factors. The environment may also affect the formed pigment in the hair itself. Saller and Maroske (1933) noted that hair tips are frequently more reddish in color than the basal portion of the hairs, and concluded that this is the result of greater exposure of the tips. Reed (1952) suggested that a sex difference in exposure (a greater proportion of the total hair length exposed in females than in males) may be responsible for the significantly greater amount of redness found in the hair of females in his sample of non-red haired individuals. The relative concentrations of the pigments in the hair may change during the lifetime of an individual. Trotter (1930), Trotter and Dawson (1934) and Bean (1935) found a greater proportion of dark haired individuals and a smaller proportion of reddish and blond haired individuals in older than in younger age groups in samples from Caucasoid populations. Reed

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[1] A dissertation submitted to the faculty of the Division of Biological Sciences, The University of Chicago, in candidacy for the degree of Doctor of Philosophy.

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(1952) found decreasing redness of the hair associated with increasing age in three adult Caucasoid individuals.

It is very probable that all brown pigments in human hair are not identical. Differences in the solubility of dark pigments from different hair in dilute base were reported by Saller and Maroske (1933) and by Keers (1934), and two brown pigments having different absorption characteristics were separated by chromatography from a solution of pigment from the hair of a single human female by Smyth, Porter and Bohren (1951). The brown pigments are melanoproteins (conjugated proteins of unknown chemical composition), reacting chemically in a manner similar to the dark melanins formed by the enzymatic oxidation of tyrosine, 3,4-dihydroxyphenylalanine (dopa) and other related phenols. The possible structure and manner of formation of natural melanins have recently been discussed by Mason (1953). The chemical nature of the reddish colored material in human hair is not clear. On the basis of the similarity between the red oxidation product of synthetic dopa-melanin and a red pigment extracted from human red hair, Arnow (1938) concluded that the red pigment is an oxidation product of brown melanin. However, Lee and Penrose (1944) extracted a red pigment by Arnow's method from the hair of an albino and from the white hair of aged persons who had been dark haired when younger. Hanna (1952) obtained, by boiling tryptophan in the presence of unpigmented nail keratin, a pigment having characteristics similar to those of the red pigment extracted by Arnow. These several observations cast doubt upon the validity of Arnow's conclusion. Flesch and Rothman (1945) found that a red phenolic-iron pigment (trichosiderin) can be extracted from cortical granules of red human hair and from blond and brown hair which has a reddish cast, but not from visibly non-red hair. They stated, however, that trichosiderin does not appear to be responsible for the red color of hair, for extraction of the compound does not materially alter the hair color.

Bunak (1939) suggested that all hair colors are due to the presence of a single melanin and that the size, number and arrangement of the melanin granules determine the visible color of the hair. Although Hausman (1928) found that the color of human hair is related to the arrangement of the pigment granules and that the color of the granules is related to their size, he thought that qualitative differences between the brown and reddish pigments, as well as differences in size and arrangement of the granules, are important in determining hair color. This latter view was also held by Danforth (1925). Conitzer (1931) found by microscopic examination that red pigment may be present in hair which appears to lack a red component, the presence of brown pigment obscuring the red so that the hair appears non-red on gross examination. Gardner and MacAdams (1934) and Reed (1952) found that the reflectance curve of definitely red hair is significantly different from that of non-red hair. Reed found, however, that the reflection spectrophotometer is no more

efficient than the human eye in discriminating between the presence and absence of small amounts of red in darkly pigmented hair.

Pigment concentration is not the only variable affecting human hair color. Keers (1934) found that the color is correlated with the diameter of the hair shaft and that the presence or absence of medullary air spaces within the hair affects the visible color. Hausman (1932, 1944) found that the number and size of the air spaces contained within the cortical layer of the hair affects the color and that a single hair may differ in color shade throughout its length because of differences in the size of the cortical vacuoles. It was suggested by Martin (1928) that the nature of the cuticular surface of the hair affects the color, a smooth surface appearing darker in color than a rough surface.

Since so many factors may affect hair color, one can not readily estimate for all of them collectively the extent to which variation in visible hair color is determined by heredity or by environment. It is possible, however, to study a single factor affecting the observable color of hair, and to estimate the degree to which this factor is affected by genetic and environmental factors.

The present study is an attempt to estimate the degree to which variation in hair pigment concentration in same-sex dizygous (fraternal) twins is determined by intra-family hereditary variation and the degree to which it is determined by intra-pair environmental variation. Because no method has been found for the quantitative separation of brown and reddish pigments, the concentration of all pigment in the hair is studied. The concentrations of solutions of pigment from the hair of twins are determined colorimetrically.[3] The variation in pigment concentration difference between members of monozygous (identical) twin pairs is compared with that between members of same-sex dizygous (fraternal) pairs, and the degree to which variation in concentration is genetically determined in the dizygous twins is estimated. In addition, estimates are made of the degrees to which pigment concentration is genetically determined in female Negroid and in male and female Caucasoid dizygous twins.

The concentrations of solutions of pigment from the hair of samples of unrelated Caucasians and Negroes are determined colorimetrically and compared. The absorption spectra of the pigments from these populations are determined by transmission spectrophotometry and compared to determine whether qualitative differences in the hair pigments may be found between racial groups.

MATERIALS

Hair samples were collected from 127 unrelated same-sex twin pairs in attendance at Chicago high schools during the school year 1942–1943. A hair

[3] Differences in the size and refractive index of the colloidal particles of different pigments in solution, as well as concentrations, may affect the colorimetric reading. It is assumed in this study that the affects of these differences are negligible.

sample of approximately 100 to 300 milligrams in amount was cut from the crown of the head of each twin with scissors and was stored in the dark in a sealed envelope. Hair was taken from both members of a twin pair on the same day. Prior to cutting, the hair on the head of each twin was classified with respect to color using the Haarfarbungtafel of Fischer (1907).

The zygosity of each twin pair was determined on the basis of (1) the A-B blood groups, (2) the M-N blood types, (3) the presence or absence of anti-Rh_o, (4) the ability to taste phenylthiocarbamide, (5) dermal ridge patterns of the fingers and palms, (6) facial and cranial measurements, (7) iris color and pattern, (8) hair color, texture and form, (9) skin color, and (10) similarity of general appearance. Only those twin pairs which were identical with respect to all blood groups and with respect to taste ability, and were strikingly similar with respect to the other criteria are considered monozygous. Of the total group of twin pairs about one-half were found to be monozygous and the other half to be dizygous.[4]

In many of the zygosity-determined pairs the amount of hair collected from one or both twins was not sufficient to permit duplicate analyses of the pair. For this reason only forty of the dizygous pairs and thirty-nine of the monozygous pairs are included in the present study. The dizygous twin sample includes sixteen male and twenty female Caucasoid pairs and four female Negroid pairs. The monozygous sample includes seven male and twenty-seven female Caucasoid pairs and five female Negroid pairs.

The hair samples of the twins have been used for comparison of the pigment concentrations and absorption curves of populations of unrelated Negroes and Caucasians as well as for the comparison of monozygous and dizygous twin pairs. To obtain samples of Negroes and Caucasians one member of each of the nine Negroid pairs and of the seventy Caucasoid pairs was chosen at random. These samples of nine unrelated Negroes and seventy unrelated Caucasians are regarded as random samples of high school age from the Chicago Negroid and Caucasoid populations.

The time between collection and study of the twin hair samples was from nine to ten years. It appeared possible that the hair would have changed in color during this period. To determine if fading had occurred, sixty samples ranging in color from blond to black were assigned Fischer grades. The color grades assigned to the samples were found to differ in eight instances from those assigned to the hair on the head at the time of collection. However, the differences were not consistently in any one direction. A difference in the method of grading may account in part for the differences in grade assigned. The absence of any systematic change in color has been taken as an indication that there has been little or no fading of the twin hair samples.

[4] The zygosity of the twin pairs was determined in conjunction with an earlier study of mental traits in twins (T. G. Thurstone, L. L. Thurstone and H. H. Strandskov, unpublished).

METHOD

As was stated earlier the primary objective of this study is to compare members of twin pairs with respect to the concentration of pigment in the hair. The concentrations are measured colorimetrically in a manner similar to that employed by Heidenthal (1940) and by Wright and Braddock (1949) in their determination of the relative concentrations of pigment from the hair of guinea pigs of different genotype. The absorption spectra desired for comparison of the pigments of Negroes and Caucasians are obtained by a method similar to that employed by Baker and Andrews (1944) in their study of guinea pig hair pigments.

The study of hair pigments by colorimetry or transmission spectrophotometry requires that the pigment be in solution and that a suitable standard be available for comparison. Russell (1939) found that the light pigment can be dissolved from yellow and reddish guinea pig hair by long hydrolysis with cold dilute base, the hair keratin being resistant to this treatment. This method of pigment solution is unsatisfactory for darkly pigmented human hair, for all of the pigment is not removed from the hair. Einsele (1938) separated the melanins from mouse hair by hydrolysis of the keratin with hot concentrated mineral acid. The melanins, which are resistant to this hydrolysis, were separated from the acid hydrolysate by centrifugation. This method has also been used by Daniel (1939) for the separation of pigments from mouse hair and by Russell (1939), Heidenthal (1940) and Wright and Braddock (1949) for the separation of pigments from black and brown guinea pig hair. In order to make colorimetric comparisons, these investigators dissolved the isolated pigments in hot dilute base. This method of solution is unsatisfactory for light colored human hair, for the error in separating pigments from the acid hydrolysate is considerable because of the small amount and flocculence of the pigment granules in the hair. In addition, a red pigment is found in the acid hydrolysates of some human hair. This appears to be a spurious pigment formed from colorless chromogens in the hair during the hydrolysis (Hanna, 1952). This pigment is present in different concentrations in the hydrolysates of different hair and may be adsorbed on the surface of the pigment granules in varying amounts. Thus erroneous estimates of pigment concentration may be obtained.

In order that the pigment concentrations of differently colored human hair may be compared, the same method of pigment solution should be used for all hair. Both the pigments and the keratin of all human hair may be rendered soluble by hydrolysis with hot dilute base, and colorimetric values for the pigments and the absorption curves of the pigments may be obtained by reading the basic hydrolysates against a standard solution.

The concentrations of hair pigments in guinea pigs were measured colorimetrically by Heidenthal (1940) and by Wright and Braddock (1949) relative

to the concentrations in the hair of guinea pigs of known genotype and color grade. Color grades of all of the guinea pigs used in both studies had been assigned previously by Wright. Because the genotypes producing different colors in human hair are not known and because different investigators may grade the same hair differently with respect to color, it was considered inadvisable in the present study to measure the concentrations relative to a given color. The colorimetric values and the absorption curves of the pigments in human hair were obtained by reading the basic solutions of hydrolyzed pigments and keratin from the hair against a standard basic solution of hydrolyzed unpigmented keratin.

A standard keratin solution was prepared by hydrolyzing unpigmented nail keratin with hot dilute base. Finger nail keratin was obtained from members of the investigator's family and from graduate students working in the laboratory. The keratin was washed with detergent and hot water and was thoroughly rinsed and dried. It was defatted in ether for a week and dried for several hours at 90 degrees Centigrade. The standards were prepared by hydrolyzing 50 milligram samples of fat-free keratin for two hours under reflux with 25 milliliters of 0.2 Normal potassium hydroxide (KOH). The solutions were returned to volume before reading.

The preparation and reading of pigment solutions

Individual hair samples were washed in a 0.1 per cent solution of commercial Dreft for one hour to remove surface oils and dirt and were rinsed repeatedly with distilled water. The samples were placed in siphon cups and were dried in an oven at 90 degrees C. for 24 hours. Each dried sample was defatted with cold distilled ether in an Underwriters' type extraction apparatus which was maintained at approximately 60 degrees C. in a water bath. It was found that constant hair weight was reached after approximately six hours of fat extraction, so all samples were treated with ether for at least eight hours. The samples were then dried for several hours at 90 degrees C. and were placed in a dessicator in the dark.

Spectrophotometric measurement was made of the base soluble pigments of all hair. Duplicate 50 mg. samples of each hair were placed in flasks and were boiled under reflux with 25 ml. of 0.2 N KOH. After two hours the hair was completely dissolved in most cases, as indicated by the absence of precipitated granules on centrifugation.[5] The solutions were returned to volume and were read immediately against a standard solution of hydrolyzed keratin. All readings were made with a Coleman Junior Spectrophotometer, Model 6-A, using matched cuvettes. Three independent readings were made of each sample at a

[5] The pigment in four samples of black hair, all from one Negro monozygous twin pair, was found resistant to this hydrolysis. Additional boiling for four hours did not completely dissolve the pigment granules in these samples. This monozygous pair is not included in this study.

wave length of 400 mμ., where maximum sensitivity for the hair pigments is obtained in the visible light band, and two independent readings were made at every 50 mμ. from 450 to 700 mμ. for a total of seven wave lengths in the visible spectrum.

In order that a bias due to prior knowledge of the zygosity and sex of a twin pair would not be introduced, the twin samples were numbered in a random fashion before the beginning of this study. These numbers were used to identify samples during the course of the work. The zygosity and sex of a pair were not known at the time of pigment concentration determination. Eight samples (two twin pairs) of similar color and a single standard solution were prepared at one time. Thus all readings on duplicate samples of one individual and on both members of a twin pair were made against the same standard. To insure independent observation of duplicate samples of the same hair and of each member of a pair of twins the samples were placed at random in numbered boiling flasks for hydrolysis and the numbered solutions were read at random. It was usually not possible during the spectrophotometric analysis to determine which samples were paired.

RESULTS

Age, exposure and hair color differences in the twin pair samples

The reliability of the comparisons of intra-pair differences of twins is determined in part by the degree to which the compared pair samples are similar with respect to variables which may affect the difference between pair members. It is therefore necessary to compare the monozygous and dizygous pair samples with respect to variables which may affect differences in hair pigmentation. Previous investigators have found that hair colors change with increasing age and on exposure. Since it is possible that pigment concentration differences are also affected by these variables, the distributions of age and exposure in the monozygous and dizygous twin pair samples are compared. Exposure of the hair probably varies throughout the year, being greater in the warm than in the cold seasons. The time of collection of a sample has therefore been taken as a measure of the degree to which the hair has been exposed, a later day of collection indicating greater exposure. The means and standard deviations of day of collection and the means and standard deviations of age in the monozygous and dizygous pair samples are given in table 1. The means of the two groups are compared using Student's t test for the significance of the difference between means and the variation in the two groups is compared using the ratio of variances, F. The two twin pair samples do not differ with respect to mean age or mean day of collection by more than might be expected by chance. The differences in variation in age and in day of collection between the two samples are not greater than might occur by chance.

The means and standard deviations of day of collection and the means and standard deviations of age of sub-samples of the monozygous and dizygous twin samples are given in table 2. Comparison of the variances in age by the test of Bartlett (1937) for the homogeneity of several variances gives a value of $\chi^2_{(7)} = 6.95$. The probability is greater than 0.30 that differences in varia-

TABLE 1. MEAN AND STANDARD DEVIATION OF COLLECTION DAY OF HAIR SAMPLES AND OF AGE IN MONTHS OF THE 39 MONOZYGOUS AND 40 DIZYGOUS TWIN PAIRS. THE DIFFERENCES BETWEEN MEANS ARE COMPARED USING STUDENT'S t TEST. THE VARIANCES [(S.D.)²] ARE COMPARED USING THE F TEST. P IS THE PROBABILITY THAT ACCIDENTS OF SAMPLING WOULD GIVE AS GREAT A DIFFERENCE BETWEEN MEANS OR AS GREAT A DIFFERENCE IN VARIATION AS OBSERVED

	TWIN PAIRS		TEST			
	MZ	DZ	t		F	
			Value	P	Value	P
Mean day of year of collection	82.9 ± 1.6 (3–24–'43)	64.2 ± 1.5 (3–5–'43)	1.31	>0.10		
Standard deviation	64.140	59.692			1.15	>0.05
Mean age in months at time of collection	186.6 ± 0.4	184.9 ± 0.4	0.35	>0.70		
Standard deviation	14.964	14.280			1.10	>0.05

TABLE 2. MEAN AND STANDARD DEVIATION OF COLLECTION DAY AND OF AGE IN MONTHS OF SUB-SAMPLES OF THE MONOZYGOUS AND DIZYGOUS TWIN PAIR SAMPLES

TWIN PAIR SUB-SAMPLE	NUMBER OF PAIRS	MEAN DAY OF YEAR OF COLLECTION	STANDARD DEVIATION	MEAN AGE IN MONTHS AT TIME OF COLLECTION	STANDARD DEVIATION
Monozygous					
Negro female	5	122.2 ± 3.0	15.1	181.2 ± 1.2	5.8
White female	27	79.9 ± 2.4	64.6	187.8 ± 0.6	16.3
White male	7	66.3 ±11.2	78.6	186.0 ± 1.4	9.5
All white	34	77.1 ± 1.9	65.7	187.4 ± 0.4	15.0
Dizygous					
Negro female	4	103.5 ± 5.7	22.6	177.0 ± 3.7	14.6
White female	20	69.1 ± 3.1	62.3	184.8 ± 0.7	13.9
White male	16	44.4 ± 3.7	58.5	187.5 ± 1.1	16.9
All white	36	58.1 ± 1.6	58.9	186.0 ± 0.4	15.1

tion in age as great as those in the sub-samples could occur by chance in samples from a single population. The differences in the mean ages of the sub-samples are not significant, except that between the mean ages of the Caucasoid monozygous and dizygous female pair samples. The t value obtained by comparison of the mean ages of these sub-samples is 2.05 ($P < 0.05$). The mean

days of collection of the sub-samples are quite variant, all differing more than might be expected by chance. The variation in day of collection of each subsample is of the same magnitude as the variation of any other subsample, for the χ^2 value obtained by Bartlett's test ($\chi^2_{(7)} = 11.83$) indicates a probability greater than 0.10 that differences in variation as great as those observed could occur by chance.

The visible hair colors in the monozygous and dizygous samples are compared. Among the Negro monozygous twins five samples of hair are black, four are dark brown and one is jet black in color. Among the Negro dizygous twins five samples are black and three are jet black. Among the Caucasoid monozygous twins 55 per cent of the hair samples are shades of brown, 41 per cent are blond, 2 per cent are black and 2 per cent are red. Among the dizygous twins 68 per cent are shades of brown, 26 per cent are blond and 6 per cent are black. There are no individuals in the dizygous twin sample with decidedly red hair. Approximately 47 per cent of the Caucasoid monozygous twin hair

TABLE 3. MEAN AND STANDARD DEVIATION OF AGE IN MONTHS OF SAMPLES OF NEGRO AND CAUCASOID POPULATIONS

POPULATION	NUMBER OF INDIVIDUALS	MEAN AGE IN MONTHS	STANDARD DEVIATION
Negro	9	180.4 ± 1.3	11.8
Caucasian	70	186.5 ± 0.2	14.8

samples and approximately 31 per cent of the Caucasoid dizygous twin samples are considered to have a definite redness. This difference in percentage of red hair is due primarily to the absence of reddish blond hair samples among the dizygous twins. Approximately 8 per cent of the blond monozygous samples have a reddish cast.

The means and standard deviations of age in the Negroid and Caucasoid population samples are given in table 3. A value of $t = 1.17$ is obtained by comparison of the mean ages of the two samples and a value of $F_{(69, 8)} = 1.56$ is obtained by comparison of the variations in age of the two samples. The differences in mean age and in variation in age in the two samples are not significant.

The nature of the keratin standard solutions

The choice of nail keratin solutions as standards for the determination of hair pigment concentration is untenable if the structural and chemical differences between the keratins of nail and hair result in different optical properties of their solutions. In order to determine whether nail keratin is optically similar to hair keratin, ten standard nail keratin solutions were compared spectrophotometrically with solutions of keratin from albino human hair

(unpigmented) and with pigmented hair solutions from which the pigment had been removed. Five solutions of albino hair, each from a different individual, were studied. These were prepared by hydrolyzing 50 mg. of fat-free albino hair with 25 ml. of 0.2 N KOH. The means and standard deviations of optical density of the nail keratin and albino hair keratin solutions at each of seven wave lengths are given in table 4. The means and the variances of the

TABLE 4. MEAN (M) AND STANDARD DEVIATION (σ) OF OPTICAL DENSITY OF SOLUTIONS OF HYDROLYZED NAIL KERATIN, ALBINO HAIR KERATIN AND KERATIN FROM PIGMENTED HAIR. THE MEAN OPTICAL DENSITIES AND THE VARIATION IN OPTICAL DENSITY OF SOLUTIONS OF ALBINO HAIR KERATIN AND KERATIN FROM PIGMENTED HAIR ARE COMPARED WITH THE MEAN OPTICAL DENSITY AND VARIATION IN OPTICAL DENSITY OF SOLUTIONS OF NAIL KERATIN

WAVE LENGTH IN MILLIMICRONS		OPTICAL DENSITIES			COMPARISON OF MEANS (t) AND VARIANCES (F)			
		Nail Keratin	Albino Hair Keratin	Keratin from Pigmented Hair	Nail Keratin and Albino Hair Keratin		Nail Keratin and Pigmented Hair Keratin	
					t	F	t	F
400	M	0.1151	0.1180	0.1178	0.81		1.02	
	σ	.0061	.0060	.0067		1.04		1.20
450	M	.0458	.0458	.0446	0		0.69	
	σ	.0037	.0020	.0044		3.29		1.42
500	M	.0185	.0192	.0183	0.40		0.14	
	σ	.0033	.0012	.0034		3.30		1.08
550	M	.0096	.0098	.0093	0.19		0.25	
	σ	.0018	.0023	.0034		1.71		3.65*
600	M	.0061	.0062	.0061	0.12		0	
	σ	.0016	.0011	.0020		2.00		1.58
650	M	.0055	.0058	.0052	0.61		0.58	
	σ	.0008	.0009	.0014		1.14		2.86
700	M	.0061	.0062	.0063	0.21		0.51	
	σ	.0009	.0009	.0009		1.00		1.13

* This is the only value of either t or F which exceeds the 0.05 probability value. The probability that a difference in variation as great as this could occur by chance is 0.03.

two solutions at each wave length are compared. Neither the mean optical densities nor the variations in optical density differ significantly at any of the wave lengths studied. Solutions of keratin from sixteen differently pigmented hairs ranging in color from blond to black were studied. Fifty mg. samples of fat-free hair were hydrolyzed with 25 ml. of 0.2 N KOH. The melanins were precipitated from the basic hydrolysates by the addition of a measured volume of concentrated hydrochloric acid. The solutions were filtered to remove the

pigment granules and the filtrates read against solutions prepared by adding the same volume of acid to 25 ml. of the basic solvent. The mean optical densities and the standard deviations of optical density of these solutions are given in table 4. The mean optical density and the variance at each wave length are compared with those of the solutions of nail keratin. The mean optical densities do not differ significantly at any wave length. The variation in optical density of the pigmented hair keratin solutions is greater at all wave lengths, due to the greater chance of technical error in the preparation of the solutions and perhaps to greater variation in keratin concentration in the solutions. The difference is significant at the five per cent level at 550 mμ. only. This one significant difference may be due to the great effective error in reading solutions of low optical density.

Each keratin standard used for colorimetric comparison in this study was read against the 0.2 N KOH used in its preparation to determine the variation

TABLE 5. MEAN OPTICAL DENSITIES AND STANDARD DEVIATIONS OF OPTICAL DENSITY OF 32 KERATIN STANDARDS READ AGAINST THE BASIC SOLVENT AT EACH OF SEVEN WAVE LENGTHS IN THE VISIBLE LIGHT BAND

WAVE LENGTH MEASURED IN MILLIMICRONS	MEAN OPTICAL DENSITY OF SOLUTIONS	STANDARD DEVIATION
400	.1158 ± .0002	.0055
450	.0458 ± .0001	.0042
500	.0193 ± .0001	.0032
550	.0096 ± .0001	.0023
600	.0062 ± .0001	.0017
650	.0056 ± .0000	.0002
700	.0064 ± .0000	.0003

in standards used for the determination of concentration in different twin pairs and different individuals. The means and standard deviations of optical density of the keratin standards at seven wave lengths in the visible light band are given in table 5.

The comparison of twin pairs

Solutions of hair pigments follow Beer's law at all wave lengths. Thus the measured optical density at any wave length is directly related to pigment concentration. One hundred times the optical density at 400 mμ. has been taken as the measure of pigment concentration in the analysis of differences between monozygous and dizygous twin pairs and between populations. The measured optical densities have been adjusted to the mean of the keratin standards at all wave lengths so that the concentration measures of any two individuals or of the two populations are directly comparable.

The degree of similarity of paired individuals with respect to a quantita-

tively measured trait x may be expressed as a function of the difference between the measured values of the two individuals ($x_1 - x_2$). If the first member of each pair is chosen at random, then in a population of pairs the differences will be normally distributed about zero. Figure 1 shows the distributions of the mean hair pigment concentrations of members of the monozygous and dizygous twin pair samples. The distributions of the differences in concentration between the two members of the monozygous and dizygous twin pairs, which are obtained if the concentration of the first studied twin of each pair is taken as x_1, are shown in figure 2.

If the errors of measurement of x_1 and x_2 are independent within each twin pair in a population of pairs, the variance of the difference between pair

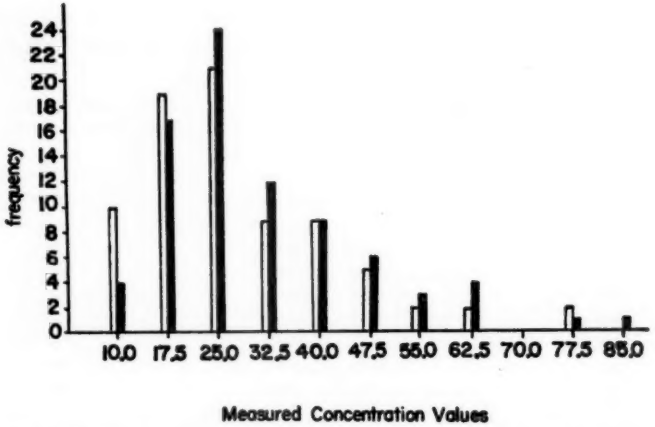

FIG. 1. The distributions of mean hair pigment concentration values in samples of monozygous and dizygous twins. The number of monozygous twins in each concentration group is indicated by the white bar and the number of dizygous twins by the solid bar.

members is equal to the sum of the independent variances of each of the members. Estimates of the variance of individuals of pairs of any population may be obtained by analysis of the total variance of the observations of that population. Comparison of the variances within pairs of any two populations (F test) will indicate whether the similarity between pair members of one is significantly greater than the similarity between pair members of the other.

In any group of twin pairs each independently measured pigment concentration value x is completely determined by the following: (1) the pair p of the population of P pairs which is represented by this measurement, (2) the twin t of the T (=2) members of the pair p, (3) the sample s of the S samples of the twin t and (4) the reading r of the R readings of the sample s. Then the measured value $x_{ptsr} = P_p + T_{pt} + S_{pts} + R_{ptsr}$. Each of these

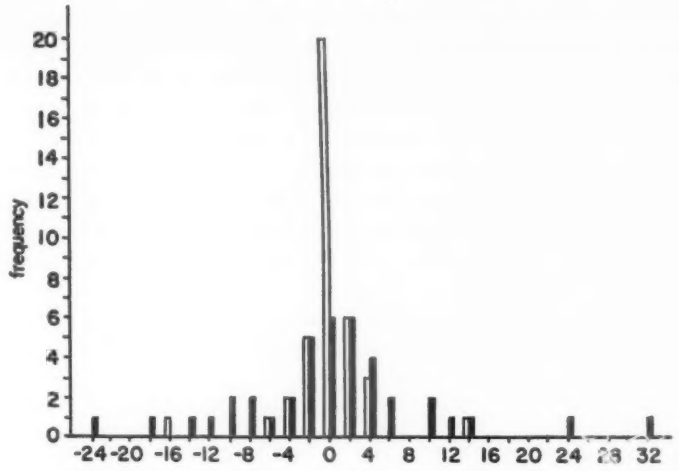

FIG. 2. The distributions of the differences in hair pigment concentration between members of monozygous and dizygous twin pairs which are obtained if the first studied member of each pair is taken as x_1. The solid bars represent dizygous pairs and the open bars the monozygous pairs.

TABLE 6. FORM OF ANALYSIS OF VARIANCE OF TWIN PAIR SAMPLES TO OBTAIN ESTIMATES OF THE VARIANCE DUE TO COLORIMETRY (σ_R^2) AND TO ERRORS IN THE PREPARATION OF SAMPLES (σ_S^2) AND OF THE VARIANCE WITHIN PAIRS (σ_T^2) AND AMONG PAIRS (σ_P^2) OF EACH OF THE MONOZYGOUS AND DIZYGOUS SAMPLES. X_{ptsr} REPRESENTS A SINGLE INDEPENDENT OBSERVATION; $X_{pts.} = \sum X_{ptsr}$; $X_{pt..} = \sum^{S} X_{pts.}$ AND $X_{p...} = \sum^{T} X_{pt..}$

VARIANCE	DEGREES OF FREEDOM	SUM OF SQUARES	VARIANCE ESTIMATED BY MEAN SQUARE
Among readings within samples	$rstp$-stp (= 8P)	$\sum^{12P} (X_{ptsr})^2 - \frac{1}{3}\sum^{4P} (X_{pts.})^2$	σ_R^2
Between samples within twins	stp-tp (= 2P)	$\frac{1}{3}\sum^{4P} (X_{pts.})^2 - \frac{1}{6}\sum^{2P} (X_{pt..})^2$	$\sigma_R^2 + 3\sigma_S^2$
Between twins within pairs	tp-p (= P)	$\frac{1}{6}\sum^{2P} (X_{pt..})^2 - \frac{1}{12}\sum^{P} (X_{p...})^2$	$\sigma_R^2 + 3\sigma_S^2 + 6\sigma_T^2$
Among pairs	P − 1	$\frac{1}{12}\sum^{P} (X_{p...})^2 - \frac{(\sum^{12P} X_{ptsr})^2}{12P}$	$\sigma_R^2 + 3\sigma_S^2 + 6\sigma_T^2 + 12\sigma_P^2$

independent random variables has variance σ^2, and $\sigma_X^2 = \sigma_P^2 + \sigma_T^2 + \sigma_S^2 + \sigma_R^2$. The total variance of a group of pair measurements may be analyzed as shown in table 6 to obtain estimates of the variance due to colorimetry (σ_R^2) and to errors in weighing and technique in the preparation of samples (σ_S^2) and of the variance of individuals within pairs (σ_T^2) and among pairs (σ_P^2).

The sums of squares and the variances estimated by analysis of the concentration values of pigment from the hair of all monozygous and dizygous twin pairs are given in table 7. Several points may be noted. The percentage of the total variance of each observation which is due to all errors in the weighing, preparation and reading of a single sample is $(\sigma_R^2 + \sigma_S^2)/(\sigma_P^2 + \sigma_T^2 + \sigma_S^2 + \sigma_R^2)$. For the sample of monozygous twins this is approximately 0.5 per cent and for the sample of dizygous twins is approximately 0.4 per cent. The percentage of the total error variance which is the result of colorimetric error is $\sigma_R^2/(\sigma_R^2 + \sigma_S^2)$. For the monozygous twins this is approximately 5.9 per cent and for the dizygous twins is approximately 3.8 per cent.

TABLE 7. DATA OBTAINED BY ANALYSIS OF VARIANCE OF HAIR PIGMENT CONCENTRATION IN SAMPLES OF MONOZYGOUS AND DIZYGOUS TWIN PAIRS

		ALL MZ TWINS	ALL DZ TWINS
Among readings within samples	Sum of squares	20.65	10.70
	d.f.	312	320
	Mean square or σ_R^2	0.0662	0.0334
Between samples within twins	Sum of squares	250.64	203.61
	d.f.	78	80
	Mean square	3.2133	2.5451
	σ_S^2	1.0490	0.8372
Between twins within pairs	Sum of squares	1723.82	12280.65
	d.f.	39	40
	Mean square	44.2005	307.0163
	σ_T^2	6.8312	50.7452
Among pairs	Sum of squares	101694.59	97886.78
	d.f.	38	39
	Mean square	2676.1734	2509.9174
	σ_P^2	219.4974	183.5751
Mean concentration value		27.8348	31.1375

The sums of squares and the variances estimated by analysis of the concentration values of pigment from the hair of the sub-samples of Caucasoid and Negroid twin pairs are given in table 8. Those estimated by analysis of the concentration values of the samples of male and female Caucasoid pairs are given in table 9. The percentage of the total variance due to experimental error ranges from approximately 0.2 per cent in the sub-sample of Caucasoid male monozygous twins to approximately 1.4 per cent in the sub-sample of Caucasoid female dizygous twins. The weighted mean percentage error in all

TABLE 8. DATA OBTAINED BY ANALYSIS OF VARIANCE OF HAIR PIGMENT CONCENTRATION IN SAMPLES OF NEGROID AND CAUCASOID MONOZYGOUS AND DIZYGOUS TWIN PAIRS

		NEGRO MZ TWINS	NEGRO DZ TWINS	ALL WHITE MZ TWINS	ALL WHITE DZ TWINS
Among readings within samples	Sum of squares	0.67	0.56	19.98	10.14
	d.f.	40	32	272	288
	Mean square or σ_R^2	0.0170	0.0175	0.0735	0.0352
Between samples within twins	Sum of squares	21.01	19.76	229.63	183.85
	d.f.	10	8	68	72
	Mean square	2.1010	2.4700	3.3769	2.5535
	σ_S^2	0.6947	0.8175	1.1011	0.8394
Between twins within pairs	Sum of squares	626.09	4160.12	1097.73	8120.53
	d.f.	5	4	34	36
	Mean square	125.2180	1040.0300	33.2645	225.5703
	σ_T^2	20.5195	172.9267	4.9813	37.1695
Among pairs	Sum of squares	7537.69	2930.44	38025.25	39886.95
	d.f.	4	3	33	35
	Mean square	1884.4225	976.8133	1152.2803	1139.6271
	σ_P^2	146.6004	—	93.2513	76.1714
Mean concentration value		56.3933	63.2708	23.6350	27.5671

TABLE 9. DATA OBTAINED BY ANALYSIS OF VARIANCE OF HAIR PIGMENT CONCENTRATION IN SAMPLES OF CAUCASOID MALE AND FEMALE TWIN PAIRS

		WHITE FEMALE MZ TWINS	WHITE FEMALE DZ TWINS	WHITE MALE MZ TWINS	WHITE MALE DZ TWINS
Among readings within samples	Sum of squares	18.75	6.28	1.23	3.86
	d.f.	216	160	56	128
	Mean square or σ_R^2	0.0868	0.0393	0.0220	0.0302
Between samples within twins	Sum of squares	223.02	116.24	6.61	67.62
	d.f.	54	40	14	32
	Mean square	4.1300	2.9060	0.4721	2.1128
	σ_S^2	1.3477	0.9556	0.1500	0.6942
Between twins within pairs	Sum of squares	1040.27	3100.19	57.46	5020.34
	d.f.	27	20	7	16
	Mean square	38.5285	155.0095	8.2086	313.7713
	σ_T^2	5.7331	25.3506	1.2894	51.9431
Among pairs	Sum of squares	32063.09	13301.65	5919.82	25598.05
	d.f.	26	19	6	15
	Mean square	1233.1958	700.0868	986.6367	1706.5367
	σ_P^2	99.5556	45.4231	81.5357	116.0638
Mean concentration value		23.7991	26.2150	23.0024	29.2573

of the sub-samples is 0.43 per cent. The percentage of error variance due to colorimetry ranges from 2.1 per cent in the sub-sample of Negroid dizygous twins to approximately 12.8 per cent in the sub-sample of Caucasoid male monozygous twins. The weighted mean percentage colorimetric error is 5.00 per cent.

The variance ratios (F) obtained by comparison of the inter-pair variances (variances among pairs) of all monozygous and all dizygous twins and of the inter-pair variances of Caucasoid monozygous and dizygous twins, and the ratios obtained by comparison of the intra-pair variances (variances within

TABLE 10. VARIANCE RATIOS (F) OBTAINED BY COMPARISON OF INTER-PAIR AND INTRA-PAIR VARIANCES OF MONOZYGOUS AND DIZYGOUS TWIN PAIR SAMPLES AND THE PROBABILITIES (P) THAT DIFFERENCES IN VARIATION AS GREAT AS OBSERVED COULD OCCUR BY CHANCE. THE TWIN GROUP HAVING THE LARGER VARIANCE IS GIVEN FIRST IN EACH CASE

COMPARISON	F	d.f.	P
Inter-pair variances			
All MZ pairs with all DZ pairs	1.20	38, 39	> 0.05
Caucasoid MZ pairs with Caucasoid DZ pairs	1.22	33, 35	> 0.05
Intra-pair variances			
All DZ pairs with all MZ pairs	7.43	40, 39	< 0.01
Caucasoid DZ pairs with Caucasoid MZ pairs	7.46	36, 34	< 0.01
Negroid DZ pairs with Negroid MZ pairs	8.43	4, 5	= 0.022
Negroid female MZ pairs with Caucasoid female MZ pairs	3.58	5, 27	= 0.015
Negroid female DZ pairs with Caucasoid female DZ pairs	6.82	4, 20	< 0.01
Caucasoid female MZ pairs with Caucasoid male MZ pairs	4.45	27, 7	= 0.028
Caucasoid male DZ pairs with Caucasoid female DZ pairs	2.05	16, 20	> 0.05

pairs) of the samples and sub-samples of monozygous and dizygous twins are given in table 10 together with the probabilities that ratios as great as those obtained could occur by chance.

The determination of concentration by heredity and environment

Within the twin pairs studied there is no variation in age or sex, for both members of each twin pair are identical with respect to these. There is no variation in exposure of the hair which may be correlated with seasonal variation, for both members of each pair were sampled at the same time. The total variation in pigment concentration in monozygous twin pairs, within which

there is no variation due to heredity, is the result of variation in environment. The variation in dizygous twin pairs is the result of both variation in environment and of intra-family variation in heredity. If the affect of environment on hair pigment concentration is independent of heredity, this variation within dizygous pairs is the sum of the intra-family hereditary variation and the intra-pair environmental variation.

If it is assumed that the variation due to environment is the same in monozygous and dizygous twin pairs, the proportions of the total variation between members of the dizygous pairs which are due to heredity and to environment may be determined. There may be considerable doubt that this assumption is valid with respect to many social or psychological traits which may be affected to different degrees by environmental factors in monozygous and dizygous twins. It is highly probable that, because of the greater general similarity between monozygous twins, their social environment and training

TABLE 11. DEGREES TO WHICH VARIATION IN HAIR PIGMENT CONCENTRATION IN DIZYGOUS TWIN SAMPLES ARE DETERMINED BY VARIATION IN INTRA-FAMILY HEREDITARY VARIATION AND BY VARIATION IN INTRA-PAIR VARIATION IN ENVIRONMENT, EXPRESSED AS PERCENTAGE OF THE TOTAL DETERMINATION

DIZYGOUS TWIN GROUP	DEGREE OF DETERMINATION	
	By Heredity	By Environment
All dizygous twins	87.19%	12.81%
All Caucasoid	86.60	13.40
Caucasoid male	97.52	2.48
Caucasoid female	77.38	22.62
Negroid female	88.13	11.87

are more similar than those of more dissimilar dizygous twins. However there is no reason to believe that this assumption is not valid with respect to a physical trait such as hair pigmentation. The variance due to heredity in dizygous twins is then

$$\sigma^2_{h_{DZ}} = \sigma^2_{T_{DZ}} - \sigma^2_{e_{DZ}} = \sigma^2_{T_{DZ}} - \sigma^2_{T_{MZ}}.$$

Wright (1921) has defined the coefficient of determination as the proportion of the total determination of a character which is due to any one causative factor in a given system of factors. Since $\sigma^2_{T_{DZ}} = \sigma^2_{h_{DZ}} + \sigma^2_{e_{DZ}}$ we may determine coefficients of determination of heredity and environment for the dizygous twins. The degrees of determination of pigment concentration by heredity and by environment in the samples of dizygous twins are given in table 11.

Comparison of Negro and Caucasian populations

The mean pigment concentration values and the sums of squares and estimated variances of the samples of Negroes and Caucasians are given in table

TABLE 12. DATA OBTAINED BY ANALYSIS OF VARIANCE OF PIGMENT CONCENTRATION IN SAMPLES OF NEGROID AND CAUCASOID POPULATIONS

		NEGROID	CAUCASOID
Among readings within samples	Sum of squares	0.64	14.99
	d.f.	36	280
	Mean square or σ_R^2	0.0178	0.0535
Between samples within individuals	Sum of squares	20.51	203.96
	d.f.	9	70
	Méan square	2.2789	2.9137
	σ_S^2	0.7537	0.9534
Among individuals	Sum of squares	8257.83	45184.78
	d.f.	8	69
	Mean square	1032.2288	654.8519
	σ_I^2	171.6583	108.6564
Mean concentration value		59.4500	36.3637

TABLE 13. MEANS AND STANDARD DEVIATIONS OF CONCENTRATION VALUES (100 TIMES OPTICAL DENSITY) OF NEGROID AND CAUCASOID POPULATION SAMPLES AT SEVEN DIFFERENT WAVE LENGTHS IN THE VISIBLE SPECTRUM

WAVE LENGTH MEASURED IN MILLIMICRONS		POPULATION SAMPLE	
		Negroid	Caucasoid
400	Mean	59.45	25.66
	σ	12.50	10.41
450	Mean	50.14	18.67
	σ	13.09	7.61
500	Mean	38.62	13.90
	σ	8.42	5.63
550	Mean	29.38	10.57
	σ	6.67	4.43
600	Mean	22.77	8.28
	σ	4.99	3.26
650	Mean	17.50	6.29
	σ	3.94	2.57
700	Mean	13.88	4.84
	σ	3.38	1.98

12. The percentage of the total variance of each reading which is due to errors in preparation and reading is 0.4 per cent in the Negro and 0.9 per cent in the Caucasian sample. The percentage of the total error of each observation

which is due to colorimetry is 2.3 per cent in the Negro and 5.3 per cent in the Caucasian sample.

A value of $F_{(8, 69)} = 1.58$ is obtained by comparison of the variances among individuals in the two populations. This value indicates a probability of greater than 0.05 that a difference in variation as great as that observed could occur by chance. A value of $t = 8.75$ is obtained by comparison of the mean concentration value of the Caucasians with that of the Negroes. The probability is less than 0.01 that a difference as great as that observed could occur by chance.

For comparison of the absorption curves of the hair pigments of the population samples the mean optical densities of the pigment solutions of each sample at each of seven wave lengths in the visible light band have been obtained. The mean concentration values (100 times the optical density) and the stand-

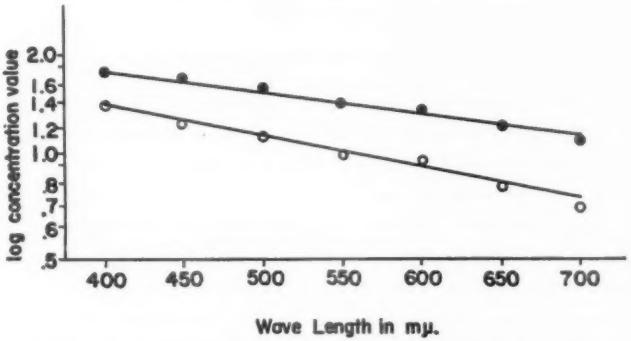

FIG. 3. Logarithms of concentration value (100 times optical density) of solutions of pigment from the hair of Negroes (dark circles) and Caucasians (open circles) plotted against wave length in millimicrons. The regression lines of the Negroes [$y = 1.46743 - .00217\ (x-550)$] and Caucasians [$y = 1.03557 - .00239(x-550)$] have been drawn in.

ard deviations of concentration value of the samples of Negroes and Caucasians are given for each wave length in table 13.

It has been shown by Daniel (1938) and by Baker and Andrews (1944) that there is an approximately linear relationship between the logarithms of optical density of solutions of hair pigments and wave length in the visible band. The logarithms of the mean concentration values of pigment from the hair of samples of Negroes and Caucasians plotted against the wave length in mμ., and the regression lines of log. concentration on wave length are shown in figure 3. The regression coefficients (b), the mean logarithms of concentration value ($\bar{y}$) and their standard errors are given in table 14.

The values of the regression coefficients in the two populations have been compared. The value $t_{(12)} = 3.88$ which is obtained indicates a probability of less than 0.01 that a difference in the slope of the regression lines as great as

that observed between the Negro sample and the Caucasian sample could occur by chance.

TABLE 14. REGRESSIONS OF THE LOGARITHMS OF MEAN CONCENTRATION VALUE (100 TIMES THE OPTICAL DENSITY) ON WAVE LENGTH IN MILLIMICRONS IN SAMPLES OF THE NEGROID AND CAUCASOID POPULATIONS. THE REGRESSIONS ARE BASED ON THE MEAN CONCENTRATION VALUES AT SEVEN WAVE LENGTHS IN THE VISIBLE LIGHT BAND. $\bar{x}$ IS THE MEAN WAVE LENGTH IN MILLIMICRONS; $\bar{y}$ THE MEAN LOGARITHM OF CONCENTRATION VALUE; $SE_{\bar{y}}$ THE STANDARD ERROR OF $\bar{y}$; b THE REGRESSION COEFFICIENT; AND SE_b THE STANDARD ERROR OF THE REGRESSION COEFFICIENT

POPULATION	$\bar{x}$	$\bar{y}$	$SE_{\bar{y}}$	b	SE_b
Negroid	550	1.46743	± .00433	−.002171	± .000043
Caucasoid	550	1.03557	± .00423	−.002388	± .000042

DISCUSSION

The reliability of the observed F *values*

The reliability of the comparisons of monozygous and dizygous pairs is dependent upon the reliability of the estimates of variance in pigment concentration in the two twin samples. The analysis of variance gives reliable estimates only if the observations in different categories are independent of each other. In the present study precautions were taken which make individual colorimetric measurements, measurements of samples from a single individual and measurements of twin pair members independent of one another. The use of the probability distribution of F for the estimation of the probability of a difference in variation is valid only if the distributions of measurements in the twin groups are normal. It is seen from figure 1 that the distributions of measurements in both the monozygous and dizygous twin samples are skewed to the right. However, the random choice of the first twin of each pair leads to a normal distribution of differences in concentration between pair members (fig. 2). The F test may be used to compare the variances of difference of the two twin groups ($F = \sigma^2_{d_{DZ}} / \sigma^2_{d_{MZ}}$). But if the errors of measurement of the twins of a pair are independent, the mean variance of each member is half the variance of the difference between pair members ($\sigma_T{}^2 = \frac{1}{2}\sigma_d{}^2$). Because there is no evidence of any relationship between colorimetric error and pigment concentration or between errors in preparation and pigment concentration, the errors of measurement may be considered independent. Then the variance ratio $\sigma^2_{T_{DZ}} / \sigma^2_{T_{MZ}}$ is equal to the ratio $\sigma^2_{d_{DZ}} / \sigma^2_{d_{MZ}}$ and the use of the probability distribution of F is justified.

Bias of the intra-pair variance ratio may result from differences between the compared twin samples with respect to variables which are correlated with the difference in pigment concentration between pair members. Although it is extremely unlikely that any compared samples would be identical with

respect to all correlated variables, it may be possible in some cases to estimate the direction of the bias introduced by lack of similarity in one or more variables. For example, it is known that human hair color changes on exposure. It is not improbable that hair pigment differences also change on exposure, the degree of change being dependent both upon the degree of exposure and upon the types and concentrations of pigments in the hairs compared. In a group of pairs of heterogeneous hair color, exposure may increase the difference in some hair shades and decrease it in others. However, differences in variation in exposure between monozygous and dizygous pairs samples may lead to greater variation in pigment concentration in one twin group relative to the other, regardless of the effect that exposure may have on pair differences. This difference in variation may lead to an F value different from that which would be obtained if the two twin samples were identical.

Trotter (1930) and others have found an increase in the proportion of dark haired individuals in older age groups, and Reed (1952) found that hair may become less red in color with increasing age. The rate of color change may not be the same for all types and concentrations of pigments. Boas and Michelson (1932) found that dark hair becomes gray at an earlier age than does light colored hair, indicating that some color changes are associated with pigmentation differences. It is possible that hair pigment differences also change with age. If this is so, then age differences in the samples of monozygous and dizygous twins will lead to a biased value of F. Greater variation in age of one sample may also cause the variation in pigment concentration of that sample to be increased relative to that of the other sample. Reed (1952) also found a sex difference in hair color. If there is a difference in the magnitude of the difference in pigment concentration between male and female twin pairs, then differences in sex distribution in compared samples may lead to biased variance ratios. The affect of sex on the difference between twins has been considered in the present study and will be discussed in a later section.

From examination of the variations in age and date of collection of the monozygous and dizygous twin pair samples (tables 1 and 2) it is seen that the F values obtained by comparison of the intra-pair variances of the samples of all monozygous and all dizygous twins, the Caucasoid monozygous and dizygous twins, the Negroid female and Caucasoid female monozygous twins and the Caucasoid male and female dizygous twins may be smaller than they would be if the compared samples were identical. The F values of the samples of Negroid monozygous and dizygous twins, the Negroid female and Caucasoid female dizygous twins and the Caucasoid male and female monozygous twins may be greater than if the compared samples were identical with respect to age and time of collection.

The mean concentration of pigment in the hair of the dizygous twins is greater than the mean concentration in the monozygous twins (table 7). This

is also the case in the sub-samples of monozygous and dizygous twins (tables 8 and 9). As has been noted previously, the affects of increasing age and of exposure on hair pigment concentration differences in twins may be correlated with the concentration of pigment in the hair. The differences in mean concentration between the monozygous and dizygous twin samples are all small except those between Negroid and Caucasoid samples. The affect of these differences on the variance ratios of the Caucasians will not be considered. The differences between Negroes and Caucasians will be discussed.

The probability is greater than 0.05 that the observed difference in inter-pair variation between samples of all monozygous and all dizygous twins could occur by chance. This indicates that in spite of differences in the age, sex and hair color distributions in the two groups, both may be regarded as drawn from the same population of twin pairs. The monozygous and dizygous Caucasoid twin samples also may be regarded as samples from the same population. The Negroid samples do not appear to represent samples from the same population, for the variation among pairs of the two groups is significantly different. This difference may be a consequence of the small size of the Negro pair samples.

Twin pair comparisons

The ratios obtained by comparison of the intra-pair variances of monozygous and dizygous twins (table 10) indicate that, among both Negroes and Caucasians, members of monozygous twin pairs are significantly more alike in hair pigment concentration than are members of dizygous pairs. The probability is less than 0.01 that a difference in intra-pair variation as great as that observed between the Caucasoid monozygous and dizygous twins could occur by chance. The observed difference in intra-pair variation between Negroid monozygous and dizygous twins is not as significant as that between monozygous and dizygous Caucasoid twins. In addition, the observed F value may be too great because of differences in age and exposure in the two Negroid twin groups. Larger samples of Negroid pairs are required if we are to determine whether there is truly a significant difference between monozygous and dizygous Negroid twins in the degree of similarity in pigment concentration.

It may be noted here that visibly red haired monozygous twins appear to be much more similar in trichosiderin concentration than do visibly red haired dizygous twins. The trichosiderin study is not included in this report because the small quantity of hair available from each twin did not permit sufficiently accurate analysis of the trichosiderin concentration. However the results obtained from the few twin pairs which were studied are of the same nature as the results obtained from the analysis of the concentration of all pigment.

The ratios obtained by comparison of the intra-pair variances of the Negroid female and Caucasoid female monozygous twins and of the Negroid female

and Caucasoid female dizygous twins are suggestive of a difference in the variation in hair pigment concentration within pairs of Negroid and Caucasoid twins. The F value obtained by comparison of the dizygous pairs is sufficiently greater than the 0.01 probability value of $F_{(4,\ 20)}$ that we may consider that, even if the observed value is too great, the intra-pair variation of the Negroid twins is significantly greater than that of the Caucasoid twins. The ratio of the intra-pair variances of the Negroid and Caucasoid monozygous pairs indicates that the samples of monozygous twins do not differ as significantly. The F value obtained by this comparison may be greater than it would be if the two samples were identical with respect to age and exposure. The probability of the difference between Negroes and Caucasians in intra-pair variation due to environmental factors only (monozygous pairs) is greater than the probability of the difference in intra-pair variation due to both environmental and genetic factors (dizygous pairs) between these groups. This suggests that the intra-family hereditary variation in Negroes may be greater than in Caucasians. However it must be remembered that the affects of environmental factors on pigment concentration may be related to the genetically determined concentrations. The difference in mean concentration between the Negroid and Caucasoid dizygous twins is greater than that between the Negroid and Caucasoid monozygous twins (tables 8 and 9). This greater difference in pigment concentration may result in a greater difference in the affect of environment between the dizygous twins than between the monozygous twins of the two races. It can not be determined from the available data whether the difference in intra-pair variation between the Negroid and Caucasoid pairs is a racial difference or is the result of differences in hair color in the two groups. The small size of the Negro samples may also be a factor affecting this apparent difference in the monozygous and dizygous pair samples.

The two racial groups differ with respect to the quality of pigment in the hair as measured by the regression of the logarithms of concentration value on wave length (table 14). The slope of the regression line of the Caucasians is significantly greater than the slope of the line of the Negroes (fig. 3). Ginsburg (1944) and Baker and Andrews (1944) found a striking difference between the curves of the logarithm of optical density plotted against wave length of solutions of pigment from the coats of dark and red guinea pigs, the slope of the curve of the solutions of pigment from red hair being greater. Since the Caucasoid sample contains a greater proportion of hairs having a visible reddish cast (red, brown and reddish blond) than does the Negroid sample, it is possible that the difference between the regression lines of the Negroes and Caucasians is the result of a greater relative concentration of reddish pigment in the hair of Caucasians. There is thus not only a difference in the concentration of pigments in the Negroid and Caucasoid twins but a difference in the types of pigment measured in twins of the two racial stocks.

The ratios of the intra-pair variances of the Caucasoid female and male monozygous pairs and of the Caucasoid female and male dizygous pairs suggest that there may be a difference in the variation in pigment concentration within male and female twin pairs. The F value obtained by comparison of the male and female dizygous pairs indicates that the intra-pair variation in male dizygous twins is not significantly greater than that in female dizygous twins. However, this F value may be smaller than it would be if the two dizygous twin samples were identical with respect to age and exposure. The F value obtained by comparison of the monozygous pairs indicates that the intra-pair variation of female monozygous twins is significantly greater than that of male monozygous twins. This F value may be greater than it would be if the two twin samples were identical, but is sufficiently greater than the 0.05 probability value of $F_{(27, 7)}$ that we may consider that a sex difference does occur in monozygous pairs.

The intra-pair variation in pigment concentration resulting from intra-pair environmental variation only (monozygous twins) is greater for female than for male twins, but the intra-pair variation resulting from both intra-pair environmental variation and from intra-family hereditary variation (dizygous twins) is approximately the same for male and female pairs. This indicates that (1) the intra-family hereditary variation of the male dizygous twins in this sample may be greater than that of the female dizygous twins, and (2) the degree to which the environment affects the difference in pigment concentration is determined in part by the sex of a twin pair. This sex difference may be due in part to a greater difference in exposure between pair members of female than of male twins of high school age or to a greater difference in the degree to which cosmetic preparations are used by pair members of female than of male twins. It is also possible that the genetic difference between males and females may result in greater differences in the hormonal balances of female than of male pair members.

The colorimetric determination of pigment concentration does not take into account qualitative differences between pigments in the hair. It does not take cognizance of any differences in the size or arrangement of pigment granules in the whole hair nor of differences in the hair structure. Thus it is quite possible that the differences observed between monozygous and dizygous twins are in no way correlated with differences between pair members with respect to visible hair color. It may be noted that hair color does appear to be related to pigment concentration, but individual hair samples of the same color may show striking concentration differences. This is especially true of hair of the same color from different racial stocks. Black and dark brown hair from Negroes was found repeatedly to have a considerably greater pigment concentration than hair of the same visible color from Caucasians. It should therefore not be assumed that the measured concentrations of pigment in

the hair of the Negroid and Caucasoid samples are correlated with visible hair color.

The determination of concentration by heredity and environment

Intra-pair variation in hair pigment concentration in dizygous twins appears to be determined primarily by variation in heredity (table 11). In the sample of all dizygous twins 87.19 per cent of the variation in hair pigment concentration is the result of intra-family hereditary variation and the remaining 12.81 per cent the result of intra-pair environmental variation. In Caucasoid dizygous twins 86.8 per cent of the variation in concentration is the result of intra-family variation in heredity, the remaining 13.4 per cent being the result of intra-pair variation in environment.

There is a sex difference in Caucasoid twins in the degree to which hereditary and environmental variation determine pigment concentration. In female dizygous twins 22.62 per cent of the variation in concentration results from intra-pair environmental variation, but in male twins only 2.48 per cent is the result of variation in environment. If the intra-family hereditary variation of the male and female dizygous twin pair samples are assumed to be equal, this indicates a very great difference in the effect of environment on the hair pigment concentration difference between female and male twins. In Negro female twins 88.13 per cent of the variation in concentration results from intra-family hereditary variation and 11.87 per cent from variation in environment. Although the intra-pair environmental variation in Negroid dizygous twins is greater than that in Caucasoid twins, the environment appears to be relatively less important in determining the pigment concentration in Negroes than in Caucasians.

It should be noted that the same factors which bias the intra-pair variance ratios also bias the estimates of σ_h^2. Thus if the observed F value is too great the coefficient of determination by heredity will also be too great. In estimating the coefficients the effects of environment and of heredity were assumed to be independent of each other. It has been seen, however, that the effect of environment on pigment concentration differences in twins may be correlated with the genetically determined concentration of pigment in the hair. The estimated degrees of determination are thus subject to several biases, and the coefficients given here should be regarded as approximations only.

Coefficients of determination by heredity obtained by the study of twins estimate the degree to which intra-family hereditary variation determines the variation in hair pigment concentration in siblings of the same sex and of the same age (dizygous same-sex twins). The degree to which variation in pigment concentration in a population is determined by hereditary variation is not the same, for in a population both inter-family and intra-family hereditary variation determine the variation in concentration. In a population having a variety

of hair colors, there may be differences in the pigments occurring in hair of different color shades. In addition, the variation in age and in exposure of the hair in a population will affect the variation in pigment concentration.

Holzinger (1929) expressed the relative contributions of heredity and environment to traits in a dizygous twins by the ratio σ_h^2/σ_e^2, which he called t^2. He determined this value from the correlation between members of monozygous and dizygous twin pairs [$t = (r_{MZ} - r_{DZ})/(1 - r_{MZ})$]. It is clear that t^2 is an estimate of $F - 1$, when $F = \sigma_{DZ}^2/\sigma_{MZ}^2$ and that $t^2/(t^2 + 1)$ is an estimate of the coefficient of determination by heredity. The t^2 for the concentration of pigment in the hair of dizygous Caucasoid twins is thus 6.46. Newman, Freeman and Holzinger (1937) compared twins with respect to many physical and mental characteristics. They found values of t^2 for physical traits ranging from 3.01 to 9.21, the lowest being the value obtained for cephalic index and the highest the value for total finger ridge count. The coefficients of determination of cephalic index and finger ridge count by heredity are then .7506 and .9021. The mean t^2 value for nine physical traits studied by these investigators is 4.61 ± 0.42. The t^2 values for cephalic index, sitting and standing height, weight, and head length and width are all smaller than the mean value. These traits may all respond to nutritional differences or differences in physical activity between twin pair members. The t^2 values for finger ridge counts on both the right and left hands are considerably greater than the mean value. These characters respond to a lesser degree to environmental factors. Holt (1953) has presented data on the dermal ridge counts of monozygous and dizygous twins. The t^2 estimated from her data is 3.21 and the degree of determination by heredity is .7622. These values are considerably smaller than those found for ridge count by Newman, Freeman and Holzinger, which suggests that perhaps the diagnosis of zygosity of some of the twin pairs used in this study was incorrect.

The measures of environmental determination indicate that the affect of environmental factors on many physical traits is great, but give no clue to the manner in which these factors may affect the development of a given trait. The environment may act continually throughout life or for only a limited period of time. Its effects may be independent of the genetic make-up of the individual or may vary with different genotypes. In the determination of dermal ridge patterns the in utero environment may be a factor influencing the penetrance of genes. The post-natal environment probably has little or no affect on the character. There can be little doubt that both pre- and post-natal environmental factors affect the cephalic index. In the determination of height and weight it is probable that the major influences are post-natal. The post-natal environment is certainly more important in the determination of hair pigment concentration. The affect of these post-natal environmental influences appears to be determined in part by the genetic make-up of the individual.

SUMMARY

1. The concentrations of pigment in the hair of monozygous and dizygous twins have been determined colorimetrically and the absorption spectra of the pigments in the hair samples of Negroes and Caucasians of comparable age have been determined by transmission spectrophotometry. The intra-pair variation in pigment concentration in the twin groups has been estimated and comparisons made of the variation within pairs of monozygous and dizygous twins.

2. Members of monozygous twin pairs are significantly more alike with respect to hair pigment concentration than are members of dizygous twin pairs.

3. There is a sex difference in the intra-pair variation in hair pigment concentration in Caucasoid twins. Members of female monozygous pairs are less alike with respect to pigment concentration than are members of male monozygous pairs. Possible reasons for this difference are suggested.

4. The intra-pair variation in pigment concentration of Negroid twins is greater than that of Caucasoid twins. Whether this is a racial difference or is the result of difference in hair color in the two populations can not be determined.

5. There is a qualitative difference in the pigments of Negroes and Caucasians. This difference may be the result of a greater relative concentration of reddish pigment in the hair of Caucasians.

6. Variation in hair pigment concentration in dizygous twins is the result primarily of intra-family hereditary variation. In a sample of Caucasoid and Negroid dizygous twins 87.19 per cent of the variation in hair pigment concentration is the result of intra-family hereditary variation and 12.81 per cent is the result of intra-pair environmental variation.

7. Intra-pair environmental variation is considerably more important in determining variation in pigment concentration in Caucasoid female than in Caucasoid male dizygous twins. In female twins 22.62 per cent of the variation in concentration results from intra-pair environmental variation but in male twins only 2.48 per cent results from variation in environment.

8. The variation in pigment concentration resulting from intra-pair environmental variation is greater in Negroid female than in Caucasoid female twins.

9. The environment is relatively less important in determining hair pigment concentration in Negroid female than in Caucasoid female dizygous twins.

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Heredity in Relation to Variable Resistance to Pulmonary Tuberculosis[1]

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In 1943, Kallmann and Reisner (4) presented their first comprehensive report on comparative twin sibship data indicative of genetically determined variations in resistance to tuberculosis. Their analysis was based on a comparison of tuberculosis expectancy rates, observed in a consecutive series of 308 twin index families by means of the Twin Family Method and computed in accordance with the principles of the Abridged Weinberg Method. The given procedure was chosen with a view to procuring a sufficient number of genetically dissimilar but epidemiologically comparable relationship groups (5, 6), and combined the technique of the usual twin study method (comparison of one-egg and two-egg twin index pairs) with that of an ordinary family study (sibs, parents, mates). The observed distribution of the different twin sibship data was interpreted as evidence of a polygenic type of inheritance.

More specifically, comparison of statistically corrected morbidity rates revealed that the tuberculosis expectancy of all blood relatives of tuberculous index cases exceeded that of the general population (table 1). The increase in the chance of developing clinical tuberculosis was strictly in proportion to the degree of blood relationship to an index case, and was particularly striking from the group of dizygotic co-twins to that of monozygotic co-twins. The difference between these two groups approximated a ratio of 2:7, since their corrected concordance rates were 25.6 and 87.3 per cent. The gene-controlled origin and relative constancy of this inter-group difference in disease expectancy were confirmed by subsequent follow-up observations and proved to be in general agreement with the most recent findings of other investigators (Diehl, 1950; Lurie *et al.*, 1952).

Another pertinent result of the original analysis was the observation that the presence or absence of tuberculosis in the parents of the twin index sibships

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[1] Presented in résumé at the annual meeting of the American Society of Human Genetics in Ithaca (September 8–10, 1952), this is the second report on the progress of a longitudinal study which has been aided substantially by grants from the Section of Morphology and Genetics of the U. S. Public Health Service and by the active cooperation of tuberculosis hospitals and clinics throughout the State of New York. Competent services in the various investigative and statistical phases of the project were rendered, at one time or another, by the following members of the departmental research staff: Dr. J. Danek, G. Ferris, L. Finger, G. Freedman, L. Gregory, Mrs. F. J. Kallmann, S. Kojan, D. Schwartz, and Dr. A. Tobler.

investigated changed the expectancy of the disease in the genetically comparable groups of full sibs and dizygotic co-twins, but not in the sample of monozygotic twin partners. In the former two groups, the corrected morbidity rates varied from 18.1 and 18.8 to 35.3 and 38.6 per cent, respectively, according to whether neither parent or at least one parent had been affected by the disease. Further subdivisions of the data—especially for the purpose of separating the sibships with one tuberculous parent from those with two tuberculous parents—were not feasible because of the statistical limitations of the original sample. A comprehensive investigation into the biological and statistical implications of this rather important problem was one of the main objectives of the subsequent extension of the study.

Equal significance was attached to a finding which resulted from a rearrangement of the original tuberculosis morbidity data obtained from the two groups of twin index pairs (monozygotic and dizygotic). In this approach, the avail-

TABLE 1. COMPARATIVE TUBERCULOSIS MORBIDITY RATES IN 308 TWIN INDEX FAMILIES (Kallmann and Reisner, Table 6)

	GENERAL POPULATION OVER 14 YEARS OF AGE	RELATIONSHIP TO TUBERCULOUS TWIN INDEX CASE					
		Mates (226)	Parents (688)	Half-sibs (42)	Sibs (720)	Dizygotic Co-twins (230)	Monozygotic Co-twins (78)
Without correction for age differences	1.08	6.2	16.6	9.5	18.9	18.3	61.5
Corrected according to Weinberg method	1.37	7.1	16.9	11.9	25.5	25.6	87.3

able data were analyzed in terms of similar or dissimilar degrees of resistance to the total tuberculosis disease process rather than in the dichotomous setting of concordance or discordance as to the clinical manifestation of the disease (presence or absence of any form of clinical tuberculosis in the co-twin). In an attempt to evaluate possibly graded variations in the total range of biological resistance factors of potential significance in the incidence and clinical course of pulmonary tuberculosis, a difference between arrested minimal tuberculosis in one twin and fatal disease in the other was thought to be no less revealing than a difference between no tuberculosis in one twin and a minimal lesion with arrest in the other.

In fact, total resistance to clinical tuberculosis was found in this type of analysis to be nearly six times as dissimilar in dizygotic as in monozygotic pairs. A rating of intra-pair dissimilarity in resistance was given to 11.5 per cent of 78 monozygotic pairs, and to 64 per cent of 230 dizygotic pairs. However, the clinical histories of many index cases were still incomplete at the time of the original analysis so that an extension of the study appeared desir-

able not only for the purpose of gaining additional years of observation for the original sample of twin index sibships, but also for that of enlarging various important subdivisions of the total series of sibships to be compared. Accordingly, the observation period available for a comparative analysis of twin histories at this time is in excess of 10 years (following the onset of the disease in one member of a pair) in the majority of twin index pairs included in the follow-up study. The present size and composition of the total series of twin pairs under observation are shown in table 2. Throughout this material, the zygosity diagnosis has been based, whenever practicable, upon direct observation, comparison of photographs and fingerprints, and a history of similarity or dissimilarity obtained from close associates. Cases in which fingerprints and direct observations could not be made have not been included in the analysis unless the remaining evidence was consistent and conclusive.

The data included in this report are related only to the comparative clinical histories of twin pairs and have been limited to concordant pairs (both monozygotic and dizygotic) and to that group of monozygotic pairs classified as discordant as to tuberculosis. The histories of the discordant dizygotic pairs will by analyzed at a later date, together with those of the sibs of both single-born and twin index cases in relation to the presence or absence of the disease in the parents.

TABLE 2. DISTRIBUTION OF CONCORDANCE IN THE PRESENT SAMPLE OF TWIN INDEX PAIRS (1953)

ZYGOSITY OF INDEX PAIR	CONCORDANT	NON-CONCORDANT	TOTAL NUMBER
Monozygotic	43	40	83
Dizygotic	30	263	293
Undetermined	4	96	100
Total number	77	407	476

A. MONOZYGOTIC AND DIZYGOTIC TWIN PAIRS CONCORDANT AS TO TUBERCULOSIS[2]

Comparison of the clinical data on all twin pairs with tuberculosis in both partners has been made in terms of intra-pair similarities and dissimilarities with respect to the entire clinical course of the disease. In addition to the salient radiographic characteristics of the lesions found at time of diagnosis, particular attention was paid to the mode of progression of the disease and its final outcome.

In comparing concordant twin partners with respect to age at onset of the

[2] A detailed analysis of the clinical data in this group of twins will be included in a later report by Dr. David Reisner.

disease (table 3), two categories were formed; namely, pairs with a difference of up to one year in their respective ages at onset (referred to as "simultaneous" onset) and those with a difference of more than one year ("non-simultaneous" onset). The ages used were either those reached at the time when the first verifiable symptoms occurred or those reached at the time when asymptomatic cases were discovered by routine roentgenographic examination. According to this classification, onset was simultaneous in 20 of the monozygotic pairs and only in 6 of the dizygotic pairs. The difference in the frequency of simultaneous onset is statistically significant ($.01 < P < .02$). Since the two twin groups have been shown to be comparable with respect to exposure (4), this difference appears to be directly related to zygosity. Thus it can be inferred that genetic differences between individuals contribute to resistance in the initial phase of clinical tuberculosis.

In an attempt to compare the degrees of intra-pair similarity in the clinical features of the *initial lesions*, a distinction has been made between the character

TABLE 3. INTRA-PAIR SIMILARITY IN DISEASE ONSET IN RELATION TO AGE AND ZYGOSITY

	SIMULTANEOUS ONSET*	NON-SIMULTANEOUS ONSET	TOTAL
Monozygotic pairs	20	23	43
Dizygotic pairs	6	24	30
All pairs	26	47	73

* Difference of up to one year.

(type of tissue response) and the anatomical extent (stage of progression) of the lesions. In the present analysis the term "initial lesion" refers to the radiographic findings at the time of diagnosis; in many instances it may represent an advanced stage of the disease.

Comparisons based on intra-pair similarity or dissimilarity in the various *pathogenetic types* of tuberculosis are precluded by the highly unequal representation of these types in the contemporary American population. In accordance with the relative frequencies usually reported, the vast majority of lesions observed in the present sample fall into the category of chronic pulmonary tuberculosis. The total series of index pairs classified as concordant as to clinical tuberculosis includes only three cases in which there has been evidence of acute hematogenous or extrapulmonary tuberculosis. Of the three pairs involved (2 monozygotic, 1 dizygotic), all have shown intra-pair dissimilarity as to the pathogenetic types displayed by the respective twin partners.

Within the main category of chronic pulmonary tuberculosis, *the character*

of the observed lesions has been classified according to the presumed pathological character of the lesions as portrayed on the X-ray film, whether predominantly exudative, productive, fibrotic or calcified. Special attention was paid to findings indicative of destructive changes with cavity formation. The purpose of this analysis was to obtain a rating system describing the "initial" defense reactions, and to relate these earlier responses to the subsequent course and final outcome of the disease. Accordingly, pairs with exudative, caseo-cavernous or fibrotic lesions in both twin partners have been classified as very similar; those with an exudative-productive lesion in one partner and either an exudative or a fibrotic lesion in the other, as moderately dissimilar; and those with clearly predominant trends toward exudation in one twin and toward fibrosis in the other, as markedly dissimilar.

The results of this tabulation (table 4) reveal that intra-pair similarity in the character of the "initial" lesions is much more frequent in monozygotic than in dizygotic pairs concordant as to tuberculosis. The difference between the two groups classified as very similar and markedly dissimilar is statistically

TABLE 4. INTRA-PAIR SIMILARITY IN THE CHARACTER OF INITIAL LESIONS

	VERY SIMILAR	MODERATELY DISSIMILAR	MARKEDLY DISSIMILAR	NOT COMPARABLE	INADEQUATE INFORMATION	TOTAL
Monozygotic pairs	23	2	8	2	8	43
Dizygotic pairs	7	3	9	1	10	30
All pairs	30	5	17	3	18	73

significant, with $.02 < P < .05$. It would appear, therefore, that genetic factors play a part in determining localized tissue responses, as represented in the characteristics of the "initial" lesions.

In appraising *the extent*, or stage of progression, of the lesions at the time of their discovery, the chosen classification follows the usual practice[3] of dividing them into minimal, moderately advanced, and far advanced cases. In all instances, of course, the anatomic extent of the "initial" lesion is dependent both upon the duration of the disease prior to diagnosis, and upon the rate of progression. In table 5, pairs are classified as very similar when the lesions of both twins fall into the same category, minimal, moderately advanced, or far advanced. Moderate dissimilarity denotes a combination of minimal and moderately advanced, or of moderately and far advanced lesions; and marked dissimilarity, a difference from minimal to far advanced lesions.

Again, intra-pair similarity of monozygotic pairs exceeds that of dizygotic

[3] Because most of this material was obtained and studied before 1950, terminology throughout this paper follows the *Diagnostic Standards and Classification of Tuberculosis*, 1940 Edition, National Tuberculosis Association.

pairs. The difference between very similar and markedly dissimilar pairs is significant with $.02 < P < .05$.

In view of these observations, it would seem desirable to obtain an overall measure for a comparison of the two zygosity groups with respect to intra-pair similarities in initial lesions. Hence, pathogenetic type, character and extent of the lesions of concordant pairs are tabulated together in table 6 in such a way that the tendency toward intra-pair similarity or dissimilarity can be used as a unit criterion of comparison. By and large, the observed differences between the two zygosity groups remain the same, irrespective of whether character and extent of the lesions are considered separately or together. It is

TABLE 5. INTRA-PAIR SIMILARITY IN APPARENT PROGRESSION PRECEDING DIAGNOSIS

	VERY SIMILAR	MODERATELY DISSIMILAR	MARKEDLY DISSIMILAR	NOT COMPARABLE	INADEQUATE INFORMATION	TOTAL
Monozygotic pairs	24	7	5	2	5	43
Dizygotic pairs	8	10	7	1	4	30
All pairs	32	17	12	3	9	73

TABLE 6. INTRA-PAIR SIMILARITY IN THE CHARACTER AND PROGRESSION OF INITIAL LESIONS

	CHARACTER AND PROGRESSION OF PATHOGENETICALLY SIMILAR LESIONS				PATHOGENETIC TYPE OF LESION UNKNOWN OR DIFFERENT	TOTAL
	Very Similar	Markedly Dissimilar	Other Degrees of Similarity	Unknown		
Monozygotic pairs	21	3	9	7	3	43
Dizygotic pairs	4	4	11	10	1	30
All pairs	25	7	20	17	4	73

clear, therefore, that in reference to the clinical features investigated, intra-pair similarity of lesions at the time of their first clinical recognition is distinctly greater in monozygotic than in dizygotic pairs.

It is especially interesting to note, that this trend toward similar initial lesions in monozygotic pairs cannot be interpreted simply as the result of their tendency to develop the disease at approximately the same age. It is shown in table 7 that in one-egg pairs the degrees of similarity in initial lesions have nearly the same distribution in the pairs with simultaneous and non-simultaneous onset.

Another finding is that in those pairs in whom concordance as to pulmonary tuberculosis has been established, no appreciable difference between the two zygosity groups can be demonstrated with respect to the quantifiable aspects

of the *clinical course* of the disease. The course is usually described as short or protracted, and for purposes of further description, one may specify the rate, constancy, and trend of the disease, for example, whether the course is rapidly downhill, or protracted with alternating progression and retrogression, *etc.* For the purpose of this comparison, several simplified numerical scales were devised to describe the course of the disease quantitatively, none of which

TABLE 7. INTRA-PAIR SIMILARITY IN THE INITIAL LESIONS OF MONOZYGOTIC TWINS IN RELATION TO AGE DIFFERENCE AT ONSET

CLASSIFICATION OF LESIONS	SIMULTANEOUS ONSET		NON-SIMULTANEOUS ONSET	
	Character	Progression	Character	Progression
Very similar	11	12	12	12
Moderately dissimilar	2	2	0	5
Markedly dissimilar	4	3	4	2
Not comparable	1	1	1	1
Not known	2	2	6	3
Total	20	20	23	23

demonstrated an appreciable difference between monozygotic and dizygotic pairs. One of these may be illustrated as follows:

Inactivated within 1 year	−4
Inactivated within 5 years	−3
Inactivated within 10 years	−2
Inactivated within more than 10 years	−1
Still active after an observation period of more than 3 years	0
Died of tuberculosis more than 10 years after onset	1
Died of tuberculosis between 5 and 10 years after onset	2
Died of tuberculosis between 1 and 5 years after onset	3
Died within 1 year after onset	4

Since a comparison of the two zygosity groups reveals no significant difference in intra-pair similarity as regards the clinical course of the disease, it is not surprising that a similar observation is made in relation to *outcome of the disease* at the end of the observation period. In this analysis (table 8), the illnesses of twin partners are classified as similar in outcome when they were in both instances (a) arrested, (b) fatal or (c) active at the time of the last observation. Dissimilarity implies any combination of these three categories. The reliability of the classification "arrested" may be judged by the length of time elapsed since a case was classified as "arrested" or "inactive" by the clinician. In the present material the average period of observation after inactivation was 6.0 years in the monozygotic and 8.7 years in the dizygotic group. Thus, most of these cases would be classified as "apparently cured."

It is indicated by the data in table 8 that similarity and dissimilarity in outcome are about equally frequent in one-egg pairs. In two-egg pairs there is

an excess of similar outcomes, but the difference between the two zygosity groups is statistically inconclusive ($P > .05$). Hence, the definite trend toward intra-pair similarity observed among monozygotic twins with respect to the initial lesions is not expressed in the outcome of the disease.

That clinical outcome has relatively little dependence upon genetic factors is also shown by the data analyzed in table 9. Even in monozygotic twins the frequency of very dissimilar outcomes, arrested and fatal, is nearly as great as the combined frequencies of similar outcomes. In fact, the given frequencies, 11:16:8, approach a ratio of 1:2:1, as would be expected in a random distribution.

TABLE 8. INTRA-PAIR SIMILARITY IN THE OUTCOME OF THE DISEASE

	SIMILAR OUTCOME	DISSIMILAR OUTCOME	TOTAL
Monozygotic pairs	20	22	42*
Dizygotic pairs	18	12	30
All pairs	38	34	72*

* In one pair, the outcome remained undetermined because of the disappearance of one member.

TABLE 9. INTRA-PAIR SIMILARITY IN OUTCOME AS RELATED TO ZYGOSITY

	SIMILARITY IN OUTCOME				INTRA-PAIR DIFFERENCE			
	Arrested Disease	Fatal Outcome	Active Disease	Total	Arrested vs. Active Disease	Arrested vs. Fatal Disease	Active vs. Fatal Disease	Total
Monozygotic pairs	11	8	1	20	4	16	2	22
Dizygotic pairs	9	9	0	18	1	10	1	12
All pairs	20	17	1	38	5	26	3	34

The majority of pairs with dissimilar outcome are found in the category "fatal-arrested." This observation is of particular interest with respect to monozygotic pairs concordant as to the disease. Obviously, even fatal tuberculosis in one twin does not preclude a statistically fair chance of arrest and survival for his genotypically identical co-twin.

At this point it would appear that the genetic similarity between monozygotic partners does not result in similarity of outcome, despite a striking similarity in the initial phase of the disease. However, when the above data on outcome are considered in the light of *age differences at the time of disease onset*, a significant relation between outcome and genetic similarity becomes apparent. The analysis presented in table 10 reveals that monozygotic pairs with and without simultaneous onset differ significantly in the ratio of similar to dissimilar outcomes, with $.001 < P < .01$. In these twins simultaneous onset was rather consistently followed by similar outcome, and non-simul-

taneous onset by dissimilar outcome, in contrast to the random distribution that might be expected.

In a closer examination of the pairs having non-simultaneous onset, comparison has been made between *the outcome in the first diagnosed twin and that in his co-twin*. The 23 monozygotic and 24 dizygotic pairs in this group were classified according to whether the outcome was the same, more favorable or less favorable in the first twin. Fatal outcome was considered as less favorable than active disease persisting at the end of the observation period, and active disease as less favorable than an arrested lesion.

TABLE 10. INTRA-PAIR SIMILARITY IN OUTCOME AS RELATED TO AGE DIFFERENCE AT ONSET

		SIMULTANEOUS ONSET	NON-SIMULTANEOUS ONSET
Monozygotic pairs	Similar outcome	14	6
	Dissimilar outcome	5	17
	Total	19	23
Dizygotic pairs	Similar outcome	3	15
	Dissimilar outcome	3	9
	Total	6	24

TABLE 11. OUTCOME IN THE TWIN WHO DEVELOPED TUBERCULOSIS FIRST

OUTCOME IN FIRST TWIN AS COMPARED WITH SECOND TWIN	MONOZYGOTIC PAIRS	DIZYGOTIC PAIRS
Same	6	15
More favorable	3	—
Less favorable	14	9
All pairs with nonsimultaneous onset	23	24

Table 11 shows that among the pairs having dissimilar outcome a twin developing tuberculosis more than a year before his partner can rarely be expected to have the more favorable outcome.

In some instances, this intra-pair difference may be explained by the fact that, with a known history of tuberculosis in one twin, the second member of a pair has a better than average chance of early diagnosis. This is confirmed by the data presented in table 12, which show that diagnosis in the first partner was more frequently made on the basis of symptoms, while in the second partner diagnosis was more frequently a result of routine examination of contacts.

The possible extent of dissimilar clinical developments observable in monozygotic pairs is exemplified by the histories of the twins in figure 1, who showed a difference of 16 years in disease onset. The twin on the right was only 18 years old when she developed a very destructive lesion with multiple cavities,

TABLE 12. COMPARISON OF FIRST- AND SECOND-DIAGNOSED TWIN PARTNER AS TO FREQUENCY OF DISCOVERY BEFORE APPEARANCE OF SYMPTOMS

		DIAGNOSIS MADE ON THE BASIS OF:		TOTAL
		Clinical Symptoms	Routine and Contact Examinations	
Monozygotic pairs	First twin	17	6	23
	Second twin	9	14	23
Dizygotic pairs	First twin	22	2	24
	Second twin	11	13	24

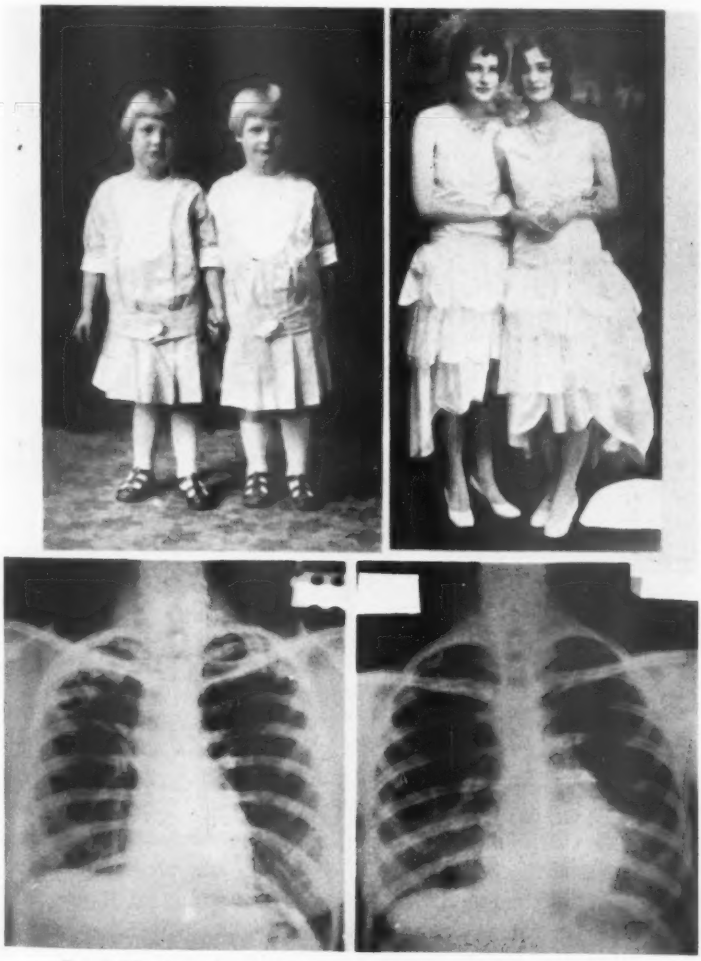

FIG. 1. Monozygotic twins dissimilar as to onset, lesions, and outcome.

and she died after seven years of slowly progressive disease. The character of her twin sister's lesion was similar but less extensive and it responded well to surgical treatment. She has been able to lead a fairly normal life for the past three years.

By contrast, the histories of the monozygotic twin sisters shown in figure 2 were notably similar in every respect. They were 24 years old when they broke down simultaneously with very similar lesions, practically identical as to

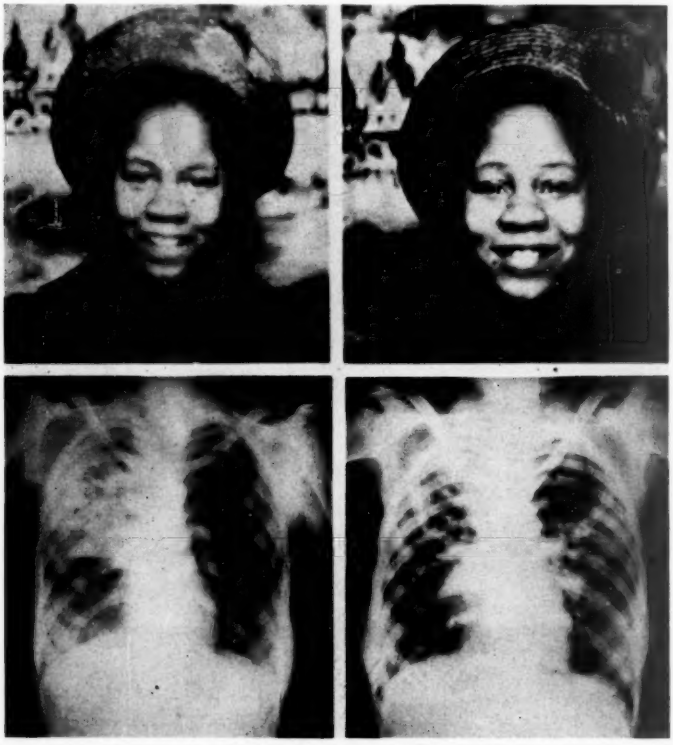

FIG. 2. Monozygotic twins similar as to onset, tuberculous lesions, and fatal outcome.

localization and with the same tendency to rapid progression. They were hospitalized together and died at the same hospital only six days apart.

A history which is typical for a large proportion of dizygotic pairs is that of the twins in fig. 3; despite pronounced differences in the early phase of the disease, the outcome was the same. Their lesions appeared eight years apart and showed marked differences in character and extent. Although the first-diagnosed twin, on the right, required more prolonged and more intensive

treatment, she finally recovered, and both sisters have been classified as apparently cured for nearly ten years.

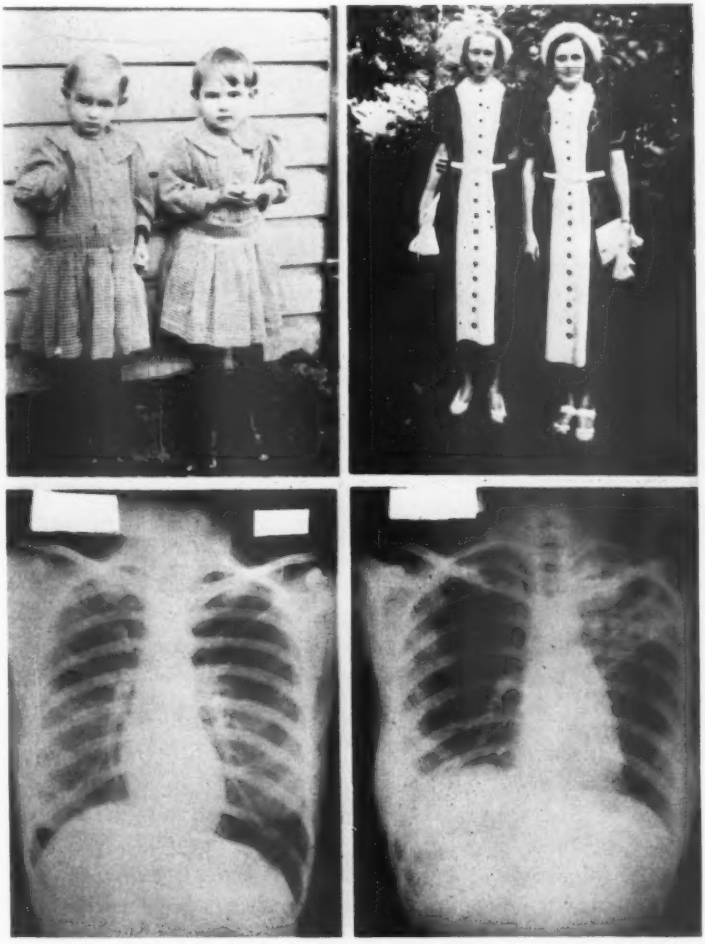

FIG. 3. Equally favorable outcome in dizygotic twins dissimilar as to onset and lesion.

Effect of Extrinsic Influences on Outcome in Concordant Pairs

In discussing concordant twin pairs, so far, explanation has been attempted in terms of genotype and constitution, i.e. intrinsic influences. In addition, of course, the clinical progress of tuberculosis is modified by extrinsic influences.

Unfortunately, most of the extrinsic factors are difficult to appraise for the

purposes of quantitative intra-pair comparisons, especially since a lack of positive information cannot be regarded as sufficient to prove the absence of modifying outside influences. Therefore, the present report will be limited to tangible intra-pair differences either in complicating pathologic conditions or in the adequacy of treatment received.

As regards adequacy of treatment, the emphasis of this analysis has been placed on promptness and continuity of institutional care. This is a relatively objective criterion which could be verified from hospital records and other official sources of information. No attempt has been made to rate the quality of medical treatment, although admittedly this may sometimes be of decisive importance.

Table 13 presents the observations on adequacy of hospitalization. Treatment has been considered as probably adequate, except in three groups of cases: a) patients known to have progressive disease, who were never hos-

TABLE 13. ADEQUACY OF HOSPITALIZATION IN RELATION TO OUTCOME

OUTCOME	ZYGOSITY	HOSPITALIZATION			
		Adequate in Both	Inadequate in Both	Inadequate in One	All Pairs
Fatal in both	MZ	2	6	—	8
	DZ	4	5	—	9
Arrested in both	MZ	8	1	2	11
	DZ	8	1	—	9
Fatal in one and arrested in the other	MZ	6	3	7	16
	DZ	3	1	6	10
All pairs		31	17	15	63

pitalized or were admitted in a moribund state; b) patients who refused hospitalization for more than six months; c) patients who interrupted hospitalization in the presence of obviously active disease.

The group of twins with fatal outcome in both partners consists largely of cases with inadequate hospitalization and rapid downhill course. In some instances, the course was so short that even with prompt hospitalization the same outcome would have been expected. Within this group, simultaneous onset occurred in nearly all the monozygotic pairs, and in none of the dizygotic pairs.

As might be expected, the pairs with inactive disease in both partners represent a contrast to the first group in therapeutic management. As seen in tables 9 and 13, there were 11 monozygotic and 9 dizygotic pairs with arrested disease in both partners. Most of them received early and continuous hospitalization although four of the cases in the dizygotic series required no hospitalization. It is of interest that in nine of the eleven monozygotic pairs, both character and extent of the "initial" lesions were practically identical. One

monozygotic pair and one dizygotic pair were very uncooperative, had minimal hospitalization and recovered only after protracted courses. In two pairs of monozygotic twins with dissimilar treatment, hospitalization was refused by one partner until the condition was far advanced.

Among the group of twins in which one partner died and the other recovered, the most interesting pairs are those in which the partners differed both in treatment and in outcome. In these 13 pairs, both monozygotic and dizygotic, the partner who received inadequate treatment died. Nine monozygotic pairs were similar as to adequate or inadequate treatment, and yet one partner died and the other recovered. In four pairs with adequate treatment, the difference in outcome appeared to be unrelated to ascertainable differences in the underlying pathology. In another pair a tension pneumothorax with pyogenic infection led to a fatal outcome in one twin, while the similar process in his co-twin became arrested after surgery. In the sixth pair with adequate treatment, the dissimilarity of outcome may be related to the type of lesion; in one twin the lesion was predominantly productive from the beginning, while in his less fortunate co-twin an initially destructive lesion progressed to a fatal outcome. In the three pairs with inadequate treatment, there was no evident reason for different outcome.

Of the seven monozygotic pairs with differences as to hospitalization, two pairs were dissimilar with respect to early complications of the tuberculous process. Generalized miliary spread occurred in one of the fatal cases, and tuberculous polyserositis in the other.

In the foregoing analysis it has been indicated that about one-fourth of the twins differed in the adequacy of hospitalization received, and they usually showed corresponding differences in outcome. On the other hand, table 13 shows that differences in outcome were also frequent among the pairs of twins both adequately or both inadequately hospitalized. It is evident that outcome of tuberculosis is dependent upon environmental factors in addition to adequacy of hospitalization; factors which do not lend themselves to this sort of statistical analysis on limited case material.

B. MONOZYGOTIC TWIN PAIRS DISCORDANT AS TO TUBERCULOSIS

Monozygotic twin pairs remaining discordant as to clinical tuberculosis are most informative if viewed as a complement to the concordant pairs. A thorough analysis of histories of pairs discordant for an extended period of observation should be of help in interpreting the dissimilar clinical developments already described in concordant pairs.

In this connection, Kallmann and Reisner (4) observed that a very low degree of resistance in the affected twins was exceptional in the discordant group. It is, therefore, interesting to examine the levels of resistance shown by these cases in the course of their disease and to identify, where possible,

any circumstances which might be responsible for intra-pair differences. The circumstances may be somewhat different from those characteristic of the concordant series.

Altogether, there were 45 pairs of one-egg twins in whom only one member was known to have tuberculosis at the end of the period of observation. Five of these pairs cannot be classified as definitely discordant because information on the co-twin was inadequate. In the remaining pairs discordance was clearly established following the onset of tuberculosis in the index case.

Kallmann and Reisner (4) computed the tuberculosis expectancy rate for the co-twins in their entire sample of monozygotic pairs. They found that only 15 per cent are likely to remain permanently free of tuberculosis. Since the possibility of later tuberculosis in a particular co-twin can never be excluded, the classification "discordant" has, at best, only a relative significance.

However, a difference between the concordant and discordant series can be demonstrated by comparing the two groups in terms of the observed period of non-concordance. For the concordant pairs this represents the average age difference at the onset of tuberculosis; for the discordant pairs it is the average period of observation following the onset in the index case. The comparative figures are, respectively, 3.6 years and 10.7 years. The area of overlap between the two groups is considerable, but it can be nearly eliminated by disregarding the non-concordant pairs observed for less than five years. Such a procedure is probably justified for the purpose of bringing out any meaningful trends in the discordant group. With this criterion, ten pairs may be excluded from further discussion. In the remaining thirty pairs the average period of observed non-concordance was 13.4 years. This group will be referred to hereafter as the discordant series.

On the whole, the discordant series represents an older group in comparison with the concordant series: the average age at onset in the discordant series was 31.5 years, while the average age at onset in the first-affected twin in the monozygotic concordant series was 22.9 years. There were 26.7 per cent index cases in whom the disease developed after the age of 35 years, while in the concordant group, there were only 11.6 per cent first-affected twin partners in whom the disease developed after the age of 35 years.

In the monozygotic discordant series the twin partners were living together without interruption before and at the time of onset of tuberculosis in 15 instances, i.e. 15 pairs are to be considered as "non-separated" before the onset. In another 15 pairs both partners were living separately for a number of years before the development of tuberculosis. The average number of years of separation before the onset of tuberculosis was 18 years; in the pairs of both monozygotic and dizygotic concordant series, separated before onset, the corresponding average was 11 years in each. This again reflects the higher average age of the discordant group.

It is interesting to compare the ratios of "separated" to "non-separated" pairs in the monozygotic group according to their concordance as to tuberculosis. There were 27 non-separated and 16 separated pairs in the concordant series, and 15 separated and 15 non-separated pairs in the discordant series. Although in the concordant group there was a greater proportion of non-separated pairs than in the discordant group, the difference is not statistically significant when a chi square test is applied ($P > 0.3$). Thus, it may be inferred that the length of the period of living together has not influenced concordance or discordance in the present sample as a group.

In the search for circumstances which may have contributed to the intrapair differences in morbidity, case histories were thoroughly examined for possible *differences in exposure* to known sources of tuberculosis. Only one instance of a clear-cut difference in exposure was found; the index case had been exposed to her husband's tuberculosis for several years. In another instance, there was a history of repeated exposure to known cases of tuberculosis in close friends. In a third pair the twins were reared in different foster homes since childhood and the index case was reported to have been exposed to tuberculosis.

Differences in living conditions obviously can be appraised only in terms of a conspicuous divergence in life histories. In some instances this may represent a difference in exposure to tuberculosis, and in other instances it may represent different types of stress. Such a marked difference in living conditions was found in a pair of male twins, one of whom had been a heavy drinker for several years and had led a very irregular life. He died of an acute perforated stomach ulcer while his tuberculosis was still active. His co-twin, although he had an early history of heavy drinking, became an abstainer and was leading an apparently normal life for several years before tuberculosis was discovered in the index case. Another pair of twins presented divergent histories beginning with separation in early childhood; the index case developed tuberculosis in a mental hospital to which he had been admitted after a history of twenty years of mental illness. In another pair of female twins, tuberculosis developed during the first pregnancy which had been preceded by several years of strenuous work. After 13 years of follow-up, during which she had two pregnancies and was living a comfortable life, the co-twin was still free of tuberculosis.

Constitutional differences can be inferred in three twin pairs. Two index cases were described as "always weaker" than their respective co-twins, although there was no evidence of significant prior illness in these cases. A constitutional, apparently non-specific vulnerability may be suspected in one twin of another pair. These twins were concordant as to schizophrenia, but tuberculosis developed in the twin whose schizophrenia did not respond to treatment and who remained hospitalized. The other, who had a spontaneous remission from his psychosis, remained free of both psychosis and tuberculosis during fifteen years of follow-up.

In three cases *identifiable pathological conditions* in the index cases preceded the onset of tuberculosis. One female index case had in childhood rheumatic fever with chorea and late menarche (age 18 years), while her co-twin had no rheumatic fever and her menarche occurred at 14. The index case was advised against entering nurses' training because of her poor health, and upon completion of her training she was found to have tuberculosis. Her co-twin, also a nurse, remained free of tuberculosis during twenty years of follow-up.

In two pairs of twins in this series, tuberculosis was associated with diabetes. In the first pair, the index case was the only one of triplets to develop tuberculosis at the age of 56 and she was also the only one of the triplets to develop diabetes. In the second of these cases both twins were diabetic, but tuberculosis developed only in the twin whose diabetes was entirely neglected.

In each of the above cases, tuberculosis occurred in the twin whose environment or constitution seemed inferior to that of the co-twin. A contrast to this is seen in two other twin pairs. Here the index cases were found in more favorable circumstances than the co-twins. The co-twin in one of these pairs was described by other members of the family as the weaker of the two since childhood. In the other pair the index case was not exposed to any unusual stresses, while his co-twin with a history of both strenuous military service and malaria remained free of tuberculosis.

It is not surprising that constitutional and situational differences between the tuberculous twin and non-tuberculous partner were found in only about half of the cases studied. Most of the extrinsic influences responsible for failure of resistance to tuberculosis are of such a nature that they go unnoticed by the patient and his family. The following two case histories exemplify discordance as to tuberculosis despite almost identical life histories.

In the first case, the twin brothers were separated for only three years, beginning at the age of 23. However, since the index case's second marriage at 26, both families have lived together. The index case worked as a tool- and diemaker, while his co-twin was a cabinetmaker. Their life situation has been very similar except for the illness of the index case. There was no other instance of tuberculosis in the family, nor any history of exposure.

The onset of tuberculosis was at the age of 43 years, at which time moderately advanced, bilateral fibrocavernous lesions were found. The course was protracted and alternating. The index case was hospitalized on several occasions during the past 42 years, with only bedrest treatment. On his last examination, at the end of the observation period, the lesion was classed as far advanced bilateral, and the disease was described as "quiescent." At the age of 85 he was in fairly good health, and able to take care of himself. His co-twin remained free of tuberculosis, and at the age of 85 was in good health, active, alert, and working in his garden.

In the second pair of male twins, there were no other cases of tuberculosis

in the family. They lived together until the age of 24. Both had practically identical life histories and situations, with no noticeable differences in susceptibility to childhood diseases. They held similar jobs, and received identical salaries. Both are married and their wives seem to have similar personalities.

The onset of tuberculosis in the index case was apparently at 27 years although he had pleurisy at 23. On first examination the lesion was far advanced, caseo-cavernous. The course of the disease was that of slow regression. Arrest of the disease was obtained with thoracoplasty three years after the diagnosis. However, cor pulmonale was diagnosed 10 years later and he died at the age of 41 of heart failure. The co-twin remained free of tuberculosis until the end of the observation period, at 45 years.

In further search for factors which may have contributed to the development of tuberculosis in only one twin of a monozygotic pair, an analysis was made of the pathologic character of the lesions as reported by the hospitals. The *relative amount of the productive component in a lesion* is generally recog-

TABLE 14. COMPARISON OF LESIONS IN CONCORDANT AND DISCORDANT MONOZYGOTIC TWINS

	PREDOMINANT TENDENCY OF LESIONS				ALL CASES
	Repair	Destruction	Mixed Lesions and Generalized Tuberculosis	Unknown	
Cases from concordant pairs	12	55	10	9	86
Cases from discordant pairs	18	8	4	—	30

nized as a measure of the capacity for healing, and indirectly as an indicator of the individual's resistance to the tuberculous process. The frequencies of the various pathologic categories of initial lesions were compared with the corresponding frequencies observed in the concordant twins in order to find out if either group showed a greater tendency to destruction or repair. This comparison must be accepted with the reservation that diagnostic criteria for the discordant series were not entirely comparable to those for the concordant pairs, on whom a single, authoritative clinician furnished all the descriptions. However, this does not seem sufficient explanation for the marked differences between the two sets of twins. In the concordant series, 13 per cent of all cases had lesions which were classified as productive, fibrous, fibro-calcific or fibro-cavernous, whereas the corresponding categories in the discordant series were represented in at least 60 per cent of all cases. The data are given in table 14.

It may also be noted that the estimate of destructive lesions in the concordant group is conservative because in a number of cases characterized by rapid downhill course the lesions were classed as of "unknown" character due to lack of adequate clinical information.

Thus, it would appear that the one-egg discordant group is characterized by a trend to repair, distinguishable even in the early clinical phase of the disease. The extent to which this represents genetically determined resistance may be indicated by Lurie's experiments with rabbits (7). In his inbred strains the tissue responses to tuberculous infection were related to the level of resistance shown by the respective strains. The resistant strains responded to the infection by a slowly progressive ulcerative pulmonary phthisis, whereas the rabbits of the susceptible strains developed an acute massive caseous pneumonia. If it is permissible to draw inferences from these experimental observations for human pathology, the respective degrees of healing shown by a lesion can be interpreted as indicating corresponding degrees of genetic resistance. Since there is an obvious preponderance of fibrotic tissue responses in the discordant twins, it can be concluded that among the discordant monozygotic pairs a high level of innate resistance is observed more frequently than in the concordant pairs. This is in agreement with the findings of Kallmann and Reisner (4).

Level of resistance can be appraised also from the *clinical course* of tuberculosis. Among the 30 discordant cases there were 13 cases with fatal termination; in another three cases the disease was still active or of undetermined activity at the end of the observation period, and in the remaining 14 cases the disease has been arrested for an adequate period. In seven of the last 14 cases the disease was of minimal extent; it became arrested on bedrest alone within 6 to 18 months, and remained arrested long enough to be considered as "apparently cured" (average of 12.7 years). In contrast to this high rate of early arrest in the discordant pairs (23 per cent), only 11 of 86 cases from the concordant series became arrested within two years.

Further inferences on the relation of the clinical course to the level of resistance can be drawn from the analysis of the cases with fatal termination. In the 1943 report (4) no fatal cases in the discordant one-egg pairs were available. Additional ten years of follow-up and further search for tuberculous index cases have made available a group of discordant pairs in which clinical developments leading to a fatal outcome can be studied.

In the concordant series, cases characterized by a rapid downhill course were singled out as a group which apparently displayed the lowest relative degree of genetic resistance in the entire sample. Patients whose disease followed a slower course presumably had a higher average resistance. This assumption is in line with the experimental findings of Lurie (7) which showed that a very protracted course of tuberculosis may indicate a higher level of genetic resistance than does a rapid downhill course. He reported that rabbits of "resistant" strains succumbed to tuberculosis after a significantly longer illness than rabbits of the less resistant strains. While his data were obtained from susceptible inbred animal strains in a controlled environment, they offer

an analogy for the hypothesis that relative resistance to tuberculosis in man may be demonstrated by a protracted, though fatal, course.

In order to compare the average duration of fatal illness between the concordant and discordant groups, the survival time in individual cases has been established by subtracting the age at onset from the age at death. As seen in table 15, there were 13 fatal cases out of 30 in the discordant group, and 34 fatal cases out of 86 in the concordant group. The average survival time of the discordant fatal cases was 7.7 years, and that of the fatal cases in the concordant group was 3.9 years. The significance of the difference between these two populations was computed by a rank method for computation of two means (9) since there was a question as to the normality of the distributions of the two groups. By this method the difference between the two populations (fatal concordant, 34 cases; fatal discordant, 13 cases) is significant at the .01 level with a t value of 3.047. The proportion of fatal cases in both the concordant and discordant series was about the same: 39.5 and 43 per cent, respectively.

TABLE 15. SURVIVAL TIME IN FATAL CASES IN CONCORDANT AND DISCORDANT MONOZYGOTIC TWINS

DURATION OF ILLNESS FROM ONSET TO DEATH	NUMBER OF FATAL CASES	
	Concordant Series	Discordant Series
Died within 12 months	16	3
Died within 2–5 years	9	4
Died within 6–10 years	7	1
Died after more than 10 years	2	5
Total	34	13

Table 15 shows, furthermore, that nearly half of the fatalities in the concordant group occurred within 12 months after the known onset of the disease, whereas the proportion of similarly brief courses in the discordant group was much smaller. On the other hand, a protracted course preceded fatal termination in only 2 of the 34 concordant cases, while in the discordant group, 5 out of 13 had a protracted course before death. Thus, it is seen that tuberculosis characterized by a very protracted alternating course, and usually with a fibro-cavernous advanced lesion, is quite common in the discordant group.

Inasmuch as the discordant group appears to be characterized by a high level of resistance, it will be of interest to search the histories of fatal cases for clinical developments or extrinsic influences which may have contributed to the fatal outcome. On examining the clinical development of the three cases with a rapid downhill course (table 15) it is found that in one of them the rapidly destructive lesion developed in the twin whose diabetes had been entirely neglected. In the second case, tuberculosis developed in an old, depressed

patient during his hospitalization in a mental institution. Only in the third case there was a distinct indication of low resistance.

Very inadequate hospitalization, usually due to refusal of treatment, was found altogether in six instances, including the third case just mentioned. As to the pathologic type of the lesion in these six cases, there were four instances

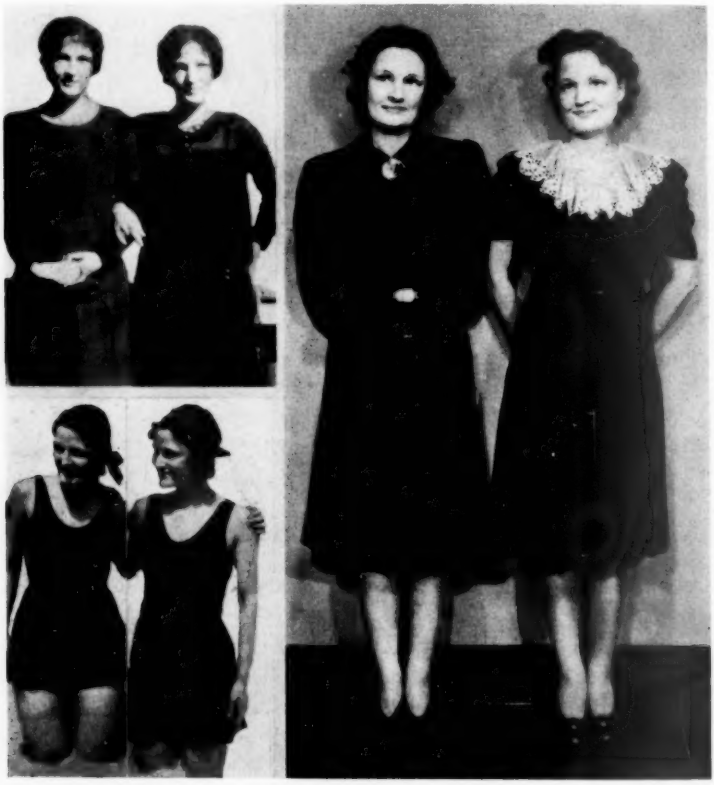

FIG. 4. Monozygotic twins (A.) discordant as to chronic (fatal) pulmonary tuberculosis and lupus vulgaris.

of caseo-cavernous or caseo-pneumonic lesions, one of predominantly productive type and one of mixed type. The last two were complicated by endobronchial involvement.

Chronic hematogenous spread was found in four other fatal cases. In two of them genito-urinary tuberculosis preceded pulmonary involvement; one of them being complicated by extensive bone tuberculosis and diabetes. A third case had in addition to pulmonary tuberculosis, tuberculous arthritis and

epilepsy. The fourth case had chronic pulmonary tuberculosis accompanied by lupus of the face. This case presented features characteristic of many histories in the discordant group. The twin sisters in this instance (figures 4 & 4a) lived together until the age of 23. There was no known exposure and no other case of tuberculosis in the family. The index case had pleurisy with effusion at 22, and pulmonary tuberculosis was recognized at 29. At the time of diagnosis, she had positive sputum and her pulmonary lesion was bilateral, moderately advanced and of a chronic fibro-caseous type. Lupus vulgaris appeared on her face at about the same time. The disease showed alternating progression and regression. Despite adequate treatment, she died at the age of 38. The

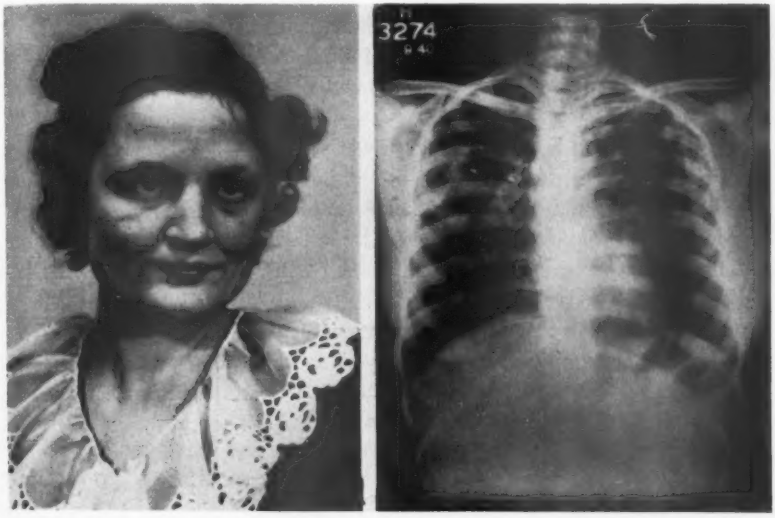

FIG. 4a. Apparently arrested lung and skin lesions in the A. twin (5 years before death).

autopsy diagnosis was: chronic tuberculosis of the lungs, tuberculous peritonitis and tuberculous enteritis. The other twin remained negative for tuberculosis for 15 years after the diagnosis of the disease in her sister. She was last seen at the age of 44.

Several fatal cases illustrate rather unusual clinical complications, some of which have already been mentioned. An example of such special clinical circumstances is provided by the following history: the index case married at 21. Two years after the marriage, her husband developed tuberculosis and stayed at home with positive sputum. Prior to the onset of her tuberculosis, the index case had three pregnancies, the first one resulting in a premature delivery, and the other two in spontaneous abortions. At the age of 26, she contracted measles, followed by a persistent cough, and shortly thereafter tuberculosis

was diagnosed. Although her condition grew worse, she refused hospitalization even after another pregnancy at 28 which was reportedly complicated by whooping cough. She was finally hospitalized at the age of 30 in a terminal stage, one month prior to death.

In another case epilepsy was reported to have interfered with treatment. In this patient post-traumatic epilepsy developed at the age of 17; tuberculosis was diagnosed at 33 with a predominantly productive lesion, later complicated by tuberculous arthritis of the shoulder. Hospitalization was adequate, but the convulsive seizures continued and were probably a detrimental factor.

On the whole, it is seen from the above analysis that three types of clinical development are most characteristic of the discordant monozygotic group; first, cases with a minimal lesion healing within a very brief period on bedrest alone; second, cases which even if terminating fatally run a very protracted alternating course; third, cases with unusual constitutional or clinical complications.

In summary it can be said that extrinsic or other special factors have been identified in many instances which might be related to the development of tuberculosis in the index case. These factors were apparently not operative in the genetically identical co-twin, who remained free of the disease throughout the observation period. It seems probable that, as a group, the discordant pairs had a higher level of genetic resistance to tuberculosis. The fact that adverse influences have not been identified in every case is to be expected from the inconspicuous nature of many such modifying factors. Of course, some pairs may have had lower resistance but remained discordant because of positive influences protecting one twin partner. Such influences, again, would go unnoticed.

C. DISCUSSION

Four sets of variables appear as most prominent in the above analysis of factors and circumstances associated with the progression of clinical tuberculosis in the concordant twin pairs: (1) zygosity; (2) age difference at onset; (3) state of the initial lesions; and (4) clinical outcome. The relations among these variables have been clarified to some extent by the present study.

The differences between the zygosity groups can be seen mainly in the frequency of simultaneous onset (table 3) and in the degree of similarity of initial lesions (tables 4, 5, and 6). Zygosity apparently did not influence either the duration of the disease or the clinical outcome (table 8). Thus, the pattern of similarity in relation to zygosity, as seen at time of diagnosis, is not maintained in later stages of the disease. Of course, outcome of the disease is the variable most remote from the onset of the disease and, therefore, may be expected to be particularly susceptible to environmental modifications.

Simultaneous onset in monozygotic pairs was followed quite consistently

by similar outcome, and conversely, there was a striking relationship between non-simultaneous onset and dissimilar outcome (table 10). In 14 of the 17 monozygotic pairs with dissimilar outcome (among the 23 pairs with non-simultaneous onset, table 11), the less favorable development occurred in the twin whose disease was discovered first. This observation is of clinical importance and is most plausibly explained on the basis of several interacting factors. Unless resistance to tuberculosis is determined completely by genotype, some monozygotic pairs are expected to have greater intra-pair differences than others. Those pairs most similar in resistance would tend to have simultaneous onset and similar outcome, while pairs with dissimilar resistance would tend to differ both in age of onset and in outcome. The more favorable outcome usually seen in the second-diagnosed twin might in part be due to an increase in resistance during early adult life, since the mean age difference at onset in these pairs is 6.3 years. Another factor to be considered is that the occurrence of tuberculosis in one member of a twin pair would lead to earlier diagnosis and treatment of the second. The validity of this explanation has been confirmed by the histories of many of our cases.

Aside from dependence on the zygosity factor, no other positive relationship has been found for the similarity of initial lesions. Thus, simultaneity of onset does not appear to enhance similarity of initial lesions (table 7), and similar lesions do not seem to be followed by similar outcome. It is shown in table 8 that clinical outcome is not influenced by the zygosity factor, i.e., there is no indication that similarity as to outcome is more pronounced in the monozygotic than in the dizygotic pairs.

Clinically of particular importance is the observation of frequent dissimilarities in resistance to progression of the disease, even in monozygotic pairs. This finding implies a considerable phenotypic range in potential responses, and thereby leaves open important opportunities for the effective application of therapeutic measures.

Apparently, similar outcome in dizygotic pairs is to be interpreted as an expression of a high degree of selection. It may be remembered that the concordant series of 30 dizygotic pairs has been drawn from a total of 293 index pairs, whereas the corresponding group of 43 monozygotic sets comes from a total of only 91 pairs. Thus, the frequent similarity of outcome in the dizygotic series may be a result of the same situations of coincidence which made these pairs concordant for presence of tuberculosis. For these reasons the concordant monozygotic and the concordant dizygotic twin samples may not be entirely comparable.

When the initial lesions differ either in pathogenetic type or in clinical character, dissimilar course and outcome are expected to be frequent. Such differences are likely to reflect a wide intra-pair variability in tissue responses, which in turn will be related to phenotypic constitution. However, an attempt

to explain the intra-pair differences in constitution in terms of genotypic and other influences would be speculative. The occurrence of such widely different clinical phenotypes as, for example, those observed in a monozygotic pair with tuberculous peritonitis in one partner and chronic pulmonary disease in the other, evidently indicates a wide range of constitutional reactions superimposed on an identical genotype. The dependence of resistance on constitution is understood here to involve not only factors specific for tuberculosis, but also many non-specific factors.

Development of clinical tuberculosis can be visualized as the result of an interaction among many components of resistance and extrinsic factors. Some of the components of the overall resistance are apparently of a non-specific nature and may be considered as general constitutional modifiers. Some of these constitutional modifiers have been tentatively identified in the analysis of the clinical course in the concordant pairs and in the discussion of circumstances leading to discordance. Of necessity, constitutional factors are here appraised mainly in terms of major pathological conditions. General constitution in the state of health still escapes meaningful appraisal in relation to tuberculosis and therefore has not been considered in the present study.

As to extrinsic influences, no definite factors have as yet been agreed upon as consistently shifting the balance between resistance and infection. Probably such influences are numerous, affecting different components in resistance. Of the unfavorable outside influences which might be considered in relation to course and outcome, inadequacy of hospitalization is only one (table 13). Adequate hospitalization, even when associated with arrest, can not be regarded as necessarily being a positive influence. The most that can be asserted is that prompt and regular treatment would tend to exclude some of the common adverse influences. There is no doubt that if the present material could be assessed in terms of the quality of treatment, more positive conclusions would be permissible.

In the present series of monozygotic twins, intra-pair similarity and dissimilarity with respect to resistance to tuberculosis can be partly accounted for in terms of genetic variations alone. It can be assumed that the investigated sample is drawn from a population of twins in which all degrees of genotypic resistance are found. Those genotypes with highest resistance would probably not develop tuberculosis and would therefore not be represented in this study. Genotypes determining somewhat less resistance would permit development of tuberculosis only under unusual circumstances. In identical twins having this level of genotypic resistance, a degree of discordance would be statistically expected. Closest to the discordant twins would be found the pairs concordant for tuberculosis, but both manifesting recovery from the disease. At successively lower levels of genotypic resistance there would be an

increasing frequency of unfavorable outcome, until in the most susceptible categories both twin partners would run a rapid downhill course.

While this is, of course, an oversimplified scheme, it is close to what may be expected on the hypothesis of a multifactorial genetic mechanism. It is probable that resistant pairs are better protected from infection, not only by a high specific resistance, but also by a favorable non-specific constitution. Even minor intra-pair divergencies in non-specific constitutional resistance may lead to different phenotypic responses and thus to discordance or at least to dissimilarity in the clinical course. In pairs with a low genotypic resistance, non-genetic differences would be unlikely to make much difference in infection or clinical course. In naturally resistant pairs the presence of tuberculosis must be a resultant of adverse environmental or constitutional factors, with respect to which monozygotic twins might easily be different.

This concept is consistent with the present observations on twins. It has been observed that in the pairs characterized by low resistance concordance tends to be quite consistent throughout the course. Discordance as to tuberculosis was in many instances associated with discordance as to other hereditary conditions like diabetes, or as to other non-hereditary pathological conditions. It is significant that it was always the twin with such a concomitant or preceding condition who developed tuberculosis. The tendency to dissimilar clinical developments observed in the monozygotic pairs with non-simultaneous onset may also be related to divergences in non-specific resistance.

According to Rife (11) variations among monozygotic twin pairs in degree of intra-pair difference are due to genotypic differences in "plasticity." With respect to tuberculosis, this plasticity may be understood as a necessary result of different degrees of genetic resistance. Experimental observations, lending further support to this view, were reported by Lurie *et al.* (8) in a study on the average numbers of human-type tubercle bacilli which rabbits of various inbred strains must inhale in order to acquire one primary focus in the lungs. A significant quantitative difference between the resistant and susceptible strains was observed. Furthermore, it was established that in a susceptible strain the individual resistance, as measured by this method, varied within relatively narrow limits; in the resistant strain the range of individual variations in resistance was significantly greater. Even if individual phenotypic differences within a litter of an inbred strain are not entirely comparable to the intra-pair differences of one-egg twins, these experiments present a rather close analogy to the findings in twins.

Two types of genetic resistance to tuberculosis are sometimes postulated. One is thought to be operative in the invasive stage and the other during the progression of the disease. In the present study, only the clinical phase has been observed, and the only conclusion that has been drawn is that any genetic

factors represented in the course and outcome are also represented at the time of clinical onset. The findings of this study are consistent with the concept of a single genetic mechanism of resistance. Intra-pair similarity in one-egg twins was most pronounced at the time of diagnosis, and decreased as the disease progressed. This divergence in the course of the disease can be interpreted as a cumulative effect of non-specific and non-genetic influences.

A more definite answer can be found in animal experiments related to the study of known components of resistance such as the rate and intensity of mononuclear or immune responses (8). These experiments show that the capacity for acquiring resistance is closely related to native resistance to initial infection. Thus, a concept which is consistent with observations both on twins and on animals is one which regards the sub-clinical and later clinical phases as depending on a single genetic mechanism of resistance.

In conclusion, the present study further elucidates the hereditary mechanism underlying resistance to tuberculosis. Although it might be difficult to demonstrate a specific hereditary mechanism with twin data alone, such data do provide some estimate of heredity as a quantitative factor. The twin data on tuberculosis reveal a significant hereditary component in resistance to the disease, and yet different monozygotic twin pairs manifest diverse constitutional responses. It therefore appears that the hereditary basis for resistance to tuberculosis is a multifactorial one, such as proposed previously by Kallmann and Reisner (4).

SUMMARY

A ten-year follow-up study has been conducted on 43 monozygotic and 30 dizygotic pairs of twins concordant as to chronic pulmonary tuberculosis, and on 40 monozygotic pairs with only one partner affected. Intra-pair similarities and dissimilarities in the "initial" stage, subsequent course and clinical outcome of the disease have been analyzed. The influence of certain modifying factors, namely adequacy of hospitalization, differences in life conditions, and non-specific constitutional factors, has been considered.

It has been found that "simultaneous" onset of the disease was more frequent in the monozygotic than in the dizygotic pairs. The extent and pathologic character of the "initial" lesions (at time of diagnosis) also were more frequently similar in the monozygotic than in the dizygotic pairs. Thus, the one-egg pairs were found to be more similar in the "initial" phase of the clinical disease than the two-egg pairs.

When the concordant one-egg and two-egg twins were compared as to intra-pair similarity in the duration of the clinical course and the outcome of the disease, no significant difference was found. In the monozygotic pairs the clinical outcome was similar or dissimilar in about equal proportions. In

most pairs the dissimilarity was between fatal outcome in one partner and arrest of the disease in the other. This indicates that even when one twin died of tuberculosis his genotypically identical partner had a statistically fair chance of survival with arrested disease. In the monozygotic pairs the majority of pairs with similar clinical outcome consisted of those pairs in which the onset was simultaneous.

While prompt and regular hospitalization was the rule in the arrested cases, and inadequate hospitalization was noted in most of the fatal cases, an unequivocal causal relationship could not be established between clinical outcome and adequacy of treatment.

In the monozygotic pairs discordant as to tuberculosis, a high level of resistance has been suggested by the prevalence of the tendency to repair in the tuberculous lesion, and by the preferential development of tuberculosis in those twin partners in whom other pathologic conditions were found, preceding or concomitant to tuberculosis. It is concluded that resistance to tuberculosis is determined by a multifactorial genetic mechanism which is significantly influenced both by non-specific heredity and by non-genetic factors.

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Severe Erythroblastosis Fetalis Caused by Sensitization to a Rare Human Agglutinogen[1]

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THE PURPOSE of this report is to describe investigations on a rare hereditable human agglutinogen discovered during the study of a puzzling case of erythroblastosis fetalis.

CASE REPORT

The patient is a female child, now 8 years old. She was the result of her mother's fourth pregnancy, and was born on October 20, 1944 at the Norwegian Hospital in Brooklyn.

The mother had never received a blood transfusion and her obstetrical history was as follows: the first child, a boy, was born at term, February 13, 1938. This baby had rectal bleeding shortly after birth, and for this he received two blood transfusions. Despite treatment he died on the sixth day. The second child, also a boy, was born at term on September 3, 1939. This baby was given a prophylactic intramuscular injection of his father's blood shortly after birth. He developed deep jaundice, but this cleared without treatment by the end of the first week of life. This boy is now 14 years old and his blood is not included in the studies which will be described, because of lack of cooperation on his part. The third pregnancy resulted in a full term female infant who was born on December 14, 1941. This baby was observed to be very pale and lived only a few hours.

When the patient was born in 1944, she appeared normal at first, but jaundice was noted 12 hours after birth. At this time a blood count showed a hemoglobin concentration of 90 per cent,[2] uncorrected W.B.C. count 40,000/cu. mm. with 35 nucleated red cells per 100 W.B.C. The baby was given a transfusion of 80 c.c. of group O, type rh blood. The following day the hemoglobin concentration had risen to 120 per cent with 5 million R.B.C./cu. mm.; at this time the uncorrected W.B.C. was 96,000 with 107 nucleated red cells per 100 W.B.C. The patient had been given prophylactic vitamin K therapy, but despite this bleeding occurred into the urine and feces, and from the nose. Therefore, on the third day the patient was given a second transfusion of 80 c.c. of group O, type rh blood. A third transfusion was given when the patient was two weeks old, and thereafter hematological recovery was uneventful.

The physical development of the child was very slow. She did not hold her head up well until she was two and a half years of age. She did not walk until she was 5 years old, and even then she fell very frequently. Her walking has been much improved during the past year. Her mother thinks that the child cannot hear, although she knows when the telephone rings. Hearing tests done recently reveal practically no hearing. She says only "ma", "bye", and "I", but in spite of this she behaves intelligently.

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[1] The authors are indebted to the father, Dr. Joseph F. Cavaliere, and to the mother and other relatives of the patient for their cooperation in providing blood samples for study.

[2] 100 per cent is equivalent to 14.5 grams hemoglobin per 100 cc.

In 1944, Rh tests had barely been introduced into clinical practice and tests for Rh antibodies had not attained their present stage of perfection. The mother was known to be Rh negative and the father Rh positive, and to this the illness of the first three children was ascribed. On this basis, however, it was not possible to explain the fourth child's (the patient) illness, because she proved to be Rh negative like the mother. Not until the anti-globulin test and the test with enzyme-treated cells were developed, could this problem be solved, as will now be described.

TABLE 1. RESULTS OF TESTS FOR Ca FACTOR ON PATIENT'S FAMILY AND UNRELATED INDIVIDUALS

BLOOD OF	A-B-O GROUP	M-N TYPE	Rh-Hr TYPE	REACTION WITH MOTHER'S SERUM*	
				Unabsorbed	Absorbed†
1. Patient (F.C.)	O	MN	rh	++	
2. Father (J.C.)	O	M	Rh_1rh		++
3. Mother (M.C.)	A	N	rh	−	
4. Paternal aunt (A.C.)	O	MN	Rh_1Rh_1		++
5. Paternal uncle (V.C.)	O	M	Rh_1rh		++
6. Paternal uncle (E.C.)	O	M	Rh_1Rh_1		−
7. Maternal grandmother (M.)	O	MN	rh	−	
8. Paternal grandfather (R.C.)	O	MN	Rh_1rh		++
9. Paternal great uncle (V.C.)	O	MN	rh	++	
10. Paternal great uncle (A.C.)	O	MN	rh	++	
11. Paternal great aunt (M.C.)	O	MN	Rh_1rh		++
12. Paternal 2nd cousin (F.M.)	O	MN	Rh_1rh		−
13. Paternal 2nd cousin (F.V.C.)	O	MN	rh	−	
14. Paternal 2nd cousin (F.A.C.)	O	MN	rh	++	
15–62. Rh-negative controls	O	various	rh	−	
63–76. Rh-positive controls	O	various	various		−
77. Rh-positive control	O				++

* All tests by the enzyme technique (ficin).

† Serum absorbed by Rh-positive cells to remove the Rh_0 antibody.

EXPERIMENTAL RESULTS

Examination of the maternal serum demonstrated, as expected, the presence of an Rh_0 antibody with an average titer of about 30 units by the anti-globulin technique and 60 units by the enzyme technique. Although the blood of the patient, 8 years old at the time of the test, was found to be Rh negative (table 1) in conformity with the original report, direct matching of the mother's serum against the baby's red cells produced clumping by the anti-globulin and enzyme techniques. At first the possibility was considered that

the child's blood might contain an Rh_0 variant, but this was excluded by tests by the anti-globulin and enzyme techniques with selected Rh_0 antisera. Thus, there could be no doubt that the child's blood belongs to type rh and not to type $\mathfrak{R}h_0$. Therefore, the mother's serum contained, in addition to anti-Rh_0, a second antibody specific for a factor present in the child's red cells but absent from her own. Unfortunately, by the time this discovery was made the titer of the second antibody proved to be quite low, namely, 4 units by the enzyme method and less than 2 units by the anti-globulin method (table 2). Since the most distinct reactions were obtained by the proteolytic enzyme[3] technique, this method was used in the further investigations, to be described.

TABLE 2. TITRATION OF Rh AND Ca ANTIBODIES IN MATERNAL SERUM

METHOD OF TITRATION	BLOOD CELLS OF	Rh-Hr TYPES§	REACTION** WITH MOTHER'S SERUM DILUTED							
			Undil.	1:2	1:4	1:8	1:16	1:32	1:64	1:128
Proteolytic enzyme*	Patient†	rh	++	+±	+	−	−			
	Mother‡	rh	−	−	−	−	−			
	Father	Rh_1rh	+++±	+++±	+++±	++	++	+±	+	−
	Control #1	Rh_1rh	+++±	+++±	+++±	++	++	+±	±	−
	Control #2	rh	−	−	−					
Anti-globulin	Patient	rh	+±	tr.	−					
	Mother	rh	−	−	−					
	Father	Rh_1rh	+++±	+++±	+++±	+++±	++	+±	tr.	−
	Control #1	Rh_1rh	+++±	+++±	++	++	+±	tr.	−	−

* The enzyme used for treating the red cells was ficin.

† Girl, 9 years of age, who had severe erythroblastosis at birth.

‡ Source of serum used in tests.

§ Mother's blood belongs to group A, the four other bloods to group O.

** The strength of the reactions is indicated by the number of plus signs, +++ being the maximum reaction possible, namely, one large clump.

In view of the low titer of the antibody it is readily understood that the reactions were delicate and not easily reproducible. Therefore, the *blind* technique was used throughout (Wiener, 1952). The tests were set up by an assistant and the readings were all taken by one of us (A.S.W.), without knowing the identity of any of the specimens whose reactions were being read. No result was accepted as final until the tests had been repeated several times in this way, and consistent results obtained.

To test further the hypothesis that the mother's serum contained two separate antibodies, absorption experiments were carried out (table 3). In these tests the mother's serum was absorbed several times with packed washed Rh-positive red cells until it lost its capacity to clump enzyme-treated Rh-positive red cells. As shown in table 2, the absorbed serum still clumped the child's

[3] The enzyme used for testing the cells was ficin, kindly provided by Merck and Co.

enzyme-treated red cells as strongly as the unabsorbed serum did, although the absorbed serum no longer clumped randomly selected red cells containing the Rh_0 and $\mathfrak{R}h_0$ factors. These results supported the conclusion that the mother's serum contained a second antibody for a rare blood factor, which we have tentatively named Ca after the patient's family name. As to be expected, absorption of the mother's serum with the patient's red cells removed the Ca antibody without affecting the Rh_0 antibodies.

Tests were then carried out on a random series of Rh-negative bloods in order to determine the frequency of the Ca factor in the population. Of 48 consecutive type rh bloods of group O,[4] not one reacted with the mother's serum. On the other hand, among the patient's relatives there were 5 individ-

TABLE 3. TITRATION OF Ca ANTIBODY BEFORE AND AFTER ABSORPTION OF MATERNAL SERUM WITH Rh-POSITIVE CELLS

	ENZYME-TREATED RED CELLS OF	Rh TYPE	REACTIONS WITH SERUM DILUTED					
			Undil.	1:2	1:4	1:8	1:16	1:32
Unabsorbed serum	Patient	rh	++	tr.	−			
	Control #1	Rh_1rh	++±	++±	++±	++	tr.	−
	Control #2	Rh_1Rh_2	++±	++±	++±	+	tr.	−
	Control #3	$\mathfrak{R}h_0$	++	tr.				
Absorbed serum	Patient	rh	++	tr.	−			
	Control #1	Rh_1rh	−	−	−			
	Control #2	Rh_1Rh_2	−	−	−			
	Control #3	$\mathfrak{R}h_0$	−	−	−			

The serum was absorbed 4 times for one hour each time, with one-third volume of packed washed Rh-positive cells. The first absorption was carried out at room temperature, the other three absorptions at body temperature.

uals belonging to type rh and the blood cells of 3 of these reacted with the mother's serum. In order to test Rh-positive bloods for the Ca factor it was necessary first to treat the mother's serum with Rh-positive blood cells in order to remove the Rh_0 antibodies. In this way it was possible to demonstrate that the father's red cells contained the Ca factor, and among 6 Rh-positive relatives as many as 4 were found to possess the Ca blood factor. On the other hand, among 15 Rh-positive bloods taken at random only one reacted with the mother's serum. Unfortunately, the donor whose blood gave a positive reaction was not available for repeat examination, so that we cannot be sure that this finding is reproducible.

In conclusion, these experiments demonstrated that the mother of our patient was sensitized not only to the Rh_0 factor, but also to a second rare he-

[4] These were kindly provided by Dr. L. J. Unger of the Blood and Plasma Exchange at N.Y.U. Post Graduate Medical School.

reditable blood factor, Ca. The patient, though Rh negative, had had erythroblastosis as a newborn infant because her red cells contained the Ca factor. It was possible to make the diagnosis after a period of 8 years because of the persistence of the Ca antibody in the mother's serum during this interval, although in low titer. Other hereditable blood factors of low frequency have been described, which were discovered in the course of investigation of puzzling cases of erythroblastosis (table 4). The case recently found by Davidsohn is outstanding because of the exceptionally high titer of the antibody, namely, approximately 256 units. Although we cannot state with certainty that the Ca factor is different from all other rare factors previously described, by comparative tests we have been able to demonstrate at least that it is

TABLE 4. RARE BLOOD FACTORS

NAME OF BLOOD FACTOR	OBSERVERS	RANDOM SERIES		FAMILY OF PROPOSITUS	
		+	−	+	−
Levay	Callender and Race (1946)	0	350	3	4
Gr.	Graydon (1946)	0	191	5	3
—	Wiener (1942)	0	ca. 500	1	3
Miltenberger	Levine et al. (1951)	0	320	4	6
Jobbins	Gilbey (1947)	0	120	2	2
Becker	Elbel and Prokop (1951)	0	272	3	4
Berrens	Davidsohn et al. (1953)	0	448	4	3
Cavaliere	Present study (type rh bloods only)	0	48	4	3

different from the Mi factor of Levine et al., as well as the blood factor of Davidsohn.

SUMMARY

The occurrence of erythroblastosis in an Rh-negative baby of an Rh-negative mother sensitized to the Rh factor is described. The presence of A-B-O blood group incompatibility was excluded. This problem remained unsolved for a period of 8 years, until the newer more sensitive techniques for detecting antibodies were introduced, namely, the anti-globulin and enzyme methods. It was then possible to demonstrate in the mother's serum, in addition to the Rh_0 antibody, an antibody for a second blood factor, Ca, present in the child's blood cells. Though this factor was not found in the blood cells of 48 consecutive type rh blood donors taken at random, it was found 4 times among 7 type rh individuals in the patient's own family. The presence of an Rh_0 variant was excluded by tests with selected $\mathfrak{R}h_0$ antisera. Thus the Ca factor appears to be a rare hereditable blood factor, probably independent of the Rh-Hr types.

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On the Inheritance of Hand and Foot Anomalies in Six Families

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INTRODUCTION

Malformations of the hands and feet are common and of many kinds. According to Gates (1946) there probably are more abnormalities of the hands and feet than of any other part of the body, with the exception of the eye.

It is true that some hand and foot anomalies are the result of accident and disease but it is equally true that many are the result of variation in heredity. The extent to which the latter is true and the mode of inheritance of those variations which have some genetic basis are questions which are not completely answered. Hence when an opportunity presented itself to study a number of different hand and foot anomalies which appeared to have a hereditary basis, it seemed worthwhile to investigate them and to present the findings. The malformations which are included are syndactyly and split hand and foot, polydactyly, and brachydactyly. Each will be considered more or less independently and in the order indicated.

A BRIEF REVIEW OF LITERATURE

1. Syndactyly and Split Hand and Foot

Syndactyly is the condition in which two or more fingers or toes are adherent or are more or less completely grown together. Split hand and foot (also called lobster claw) is a deformity in which the central digits of the hands and/or feet are lacking. It may represent an extreme variant of syndactyly.

According to Lewis (1909) a description of split hand and foot is difficult because of the great variation in the deformity even within the same family. According to him the most common lesion is one in which the hand or foot is bilaterally symmetrical, the cleft falling at the normal location of the second or third digit. He adds that the portions of the foot separated by the cleft are usually welded by skin or bony fusion into a single mass, conical in form, and terminating in one or more digital points. Lewis also states that the variation is greater in the hands than in the feet. In the presence of malformed feet, the hands may be normal, polydactylous, or syndactylous. Syndactyly is the rule, either by bone or soft tissues. Affected hands have never been recorded in the absence of foot lesions.

Cook (1935) found a wide variation of expression of a gene in a family in

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which the deformity ranged from webbing between two fingers to the extreme lobster-claw form. In this case, the assumption was that modifying factors were involved which tended to alter the expression of the dominant lobster-claw gene.

According to Popenoe (1937), the most typical split hand deformity is one in which the central digits of the hands are suppressed with an overgrowth of the marginal ones resulting in the resemblance to a lobster's claw—hence, the common name which is sometimes applied. As to the transmission of the gene, Popenoe states that it is simplest to think of a single main gene as involved within a given family. The difference in manifestation being due to the influence of modifying genes that are different in each case but somewhat constant from one generation to another. In different families different genes may possibly be responsible for similar effects.

Wightman (1937) reported a case of syndactyly in a family in which the gene for the abnormal condition was completely dominant to the normal one, but varying in expression.

Syndactyly was reported by Bailey (1938) in six generations of a family in which the deformity was regarded as due to a simple dominant gene with variable expression. The anomalies observed in this particular family varied from four ordinary shaped fingers to the extreme condition of only two digits.

A case was reported near Bombay, India, by Hegdekatti (1939) which apparently came into being as the result of a recent mutation. The affliction involved both the hands and the feet with the gene behaving as a simple dominant. There was some variation in degree of malformation with the offspring exhibiting varying degrees of expression uncorrelated with the expression in the parents.

Potter and Nadelhoffer (1947) described the split foot deformity in a family as being one in which there was an absence or extreme hypoplasia of the central metatarsal bones, absence of the phalanges normally found distal to those metatarsals, and a soft tissue disturbance leading to fusion of the medial and lateral digits into two masses. The third and fourth metatarsal bones they found to vary from normal to complete absence. The terminal phalanges were set at such an angle that they turned toward each other, giving the appearance from which the lobster claw deformity takes its name.

2. Polydactyly

The possession of supernumerary digits on the hands and feet is a hereditary characteristic which shows great variation. Brandeis (1915) reported such a case in a family. The parents were cousins with neither possessing the extra finger or toe, and with no evidence of the trait having ever existed. Out of six children, the abnormality appeared in three, with the extra digits being either on one hand, both hands, or on both hands and feet. The normal

as well as the afflicted children transmitted the defect. Brandeis concluded that the trait was probably due to an irregularly dominant gene, but the evidence is not conclusive.

According to Milles (1928), there are three principal types of polydactyly. In the first type, the extra digit takes the form of a small fleshy mass with a true fingernail and is attached by a mere pedicle to the lateral margin of the fifth digit in the region of the first phalangeal joint. The second type includes those supernumerary digits appearing as a complete duplication of the fifth. Anomalies of type three are those reported as being duplication of the pollex. This form is quite rare. According to Milles all of these types are transmitted as Mendelian dominants.

An unusual case of polydactyly was reported by Penhallow (1928) in which the hands were symmetrical, but in the place of each thumb there were two completely formed digits resembling the third and fourth fingers respectively. Each digit was separate from the others and was completely formed, even to the extent of having separate metacarpals. These extra fingers functioned independently, and could be individually flexed and extended. As to the feet, the right foot was normal, but the left had a double great toe.

Polydactyly appears to be transmitted by an irregular dominant gene in most instances. However, Snyder (1929) reported several Negro families in which the condition was found to be recessive. His material includes 171 individuals of which 54 possessed an extra digit.

A family was described by McClintic (1935) in which extra fingers and toes appeared in five generations. The condition occurred in approximately half the offspring of afflicted parents, but all normal parents produced normal offspring. Hence the condition was attributed to a simple dominant gene.

Jackson (1937) reported a polydactylous family in North Dakota in which most of the members had six fingers and six toes. Some had the extra digits on hands only, some on feet only, and a few on one hand or one foot. The gene behaved as an irregular dominant.

A Negro family in which supernumerary digits occurred was reported by Callan (1942). The variations in the expression of the gene in this particular case were extra toes, extra little fingers, and extra thumbs. The defect appeared to be dependent upon an irregular dominant gene.

Pipkin and Pipkin (1946) reported a case of polydactyly of feet only in which the mode of inheritance did not appear to be the usual one. They suggested that this case of polydactyly was dependent upon the simultaneous presence of two dominant genes, one being rare in the population, the other common.

3. Brachydactyly

Brachydactyly is the abnormal shortness of the fingers and toes. Another definition is the occurrence of short fingers or toes due to shortness of the

finger bones or to the absence of one of the phalanges. Brachymetapody is a related condition in which the metacarpals or metatarsals are abnormally short.

Brachydactyly is a congenital anomaly which is usually transmitted as a simple Mendelian dominant. Breitenbecker (1923) reported a family in which the terminal phalanx of the thumb of affected individuals was shortened and thickened. The mutation probably arose five generations previous to the time of the writing of the paper.

Hefner (1924) reported several cases of brachydactyly in which it was the terminal phalanx of the thumb which was affected. The trait was reported to be a simple Mendelian dominant.

According to Cutter and Nelson (1931), brachydactyly was one of the first Mendelian traits found in human beings. The anomaly occurring in the family reported by them was found only in the feet, and in each case appeared as a simple dominant. In other families the condition may occur in the hands or the feet only or in both hands and feet.

In a family reported by Gillette (1931) the metacarpals of the third fingers on both hands were shortened. In all cases, the defect was not observed in any individual until he or she was seven years of age. The trait was transmitted as a Mendelian dominant.

For purposes of comparison, Nissen (1933) divided the condition termed brachydactyly into two groups. The first group is a somewhat heterogenous one in which any of the phalanges or metacarpals are shortened, either singly or in various combinations. In group two, the basic condition consists of a shortening of the middle phalanges in all the fingers and toes. He reported several families possessing the brachydactylous anomaly. The gene in each case behaved as a simple dominant.

Koenner (1934) reported a case of brachymetapody in which the fourth finger of the left hand hardly reached to the second joint of the second finger.

Sayles and Jailer (1934) presented a case of four generations of individuals with short thumbs. The terminal phalanx of the thumb was shortened and somewhat widened, resulting in a squatty appearance of the whole digit.

Five generations of short digits in a large family in West Virginia were reported by Walter (1938). The expression of the gene varied from one in which a few or all fingers or toes were short to one in which both fingers and toes were short. The trait was inherited as a simple Mendelian dominant.

According to Stiles (1939), brachymetapody is a relatively rare anomaly. In a family of four generations reported by him only the fourth metacarpal of the left hand was affected, with the feet being normal. The affected metacarpal of the left hand was from birth about two-thirds as long as the corresponding one in the right hand. The defect in this particular family was reported as being transmitted as an irregular dominant.

Cohn and Ravin (1941) reported an unusual case of brachydactyly in which the character was transmitted as a recessive trait rather than as a dominant one. The condition appeared as a bilateral, symmetrical shortening of the index fingers and first toes. The hands and feet were normal in every other respect.

An interesting case of brachymetapody was presented by Steggerda (1942). In this particular family, the metatarsals on both feet were the only parts affected, the hands being normal. The trait was transmitted as a simple dominant.

Birch-Jensen (1949) published results of investigations made to include all of the patients with congenital deformities of the upper extremities in Denmark that were born before January 1, 1947. Some of the deformities reported are split-hand, split hand and syndactyly, brachydactyly, and symbrachydactyly (webbed shortened fingers). He reported split hand with or without syndactyly to be inherited as a dominant gene. He gave the inheritance of brachydactyly as dominant while symbrachydactyly, when inherited, seemed to be inherited as a recessive gene.

PRESENTATION AND DISCUSSION OF SIX PEDIGREES STUDIED

The following pedigrees were obtained as a result of personal interviews and examinations. Some of the affected individuals or members of affected families were college students. Others lived in the community of the investigators or in near-by towns.

In figure 1 is shown a five generation pedigree (Pedigree No. 1) for split hands and feet in which there is also found an occurrence of syndactyly. The split hand and foot defect varies in this family from one hand and one foot being affected (II-1) to the extreme condition of both hands and both feet being in the form of lobster-claws (IV-4).

The two hands of the same individual may differ as may be observed from the photograph of the hands of IV-4 shown in plate 1. In this individual the cleft occurs in both hands between the second and fourth digits, with the central digit in each hand being suppressed. The fifth digits in both hands are, with the exception of being slightly crooked, very nearly normal. The fourth digits appear entirely normal.

On the right hand of IV-4 both the first and second metacarpals are separately formed, but the bases of the first and second phalanges are fused, resulting in digits that are covered by a single conical mass of flesh with a double nail, one for each digit.

The first and second metacarpals of the left hand of IV-4 are fused, but only one digit is present consisting of two phalanges. A small median cleft appears in the distal phalanx, but there is only one nail on the digit. No abnormality of the carpus was demonstrated in the X-ray photograph.

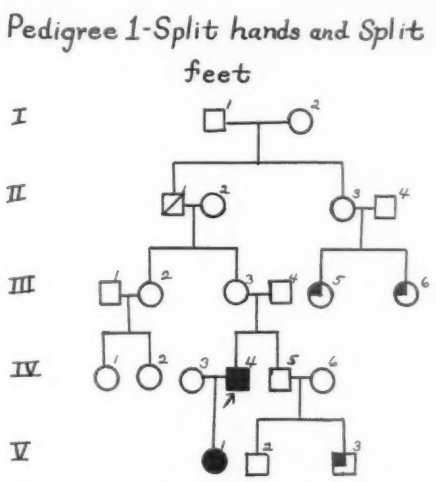

FIG. 1. A five-generation pedigree showing split hands and split feet

SYMBOLS USED IN PEDIGREES

- Normal male
- Normal female
- Male with deformity in both hands and feet
- Female with deformity in both hands and feet
- Male with slight malformation
- Female with slight malformation
- Split feet and malformed hands
- Male still born
- Female still born
- Lobster claw in one hand
- Polydactyly in both hands of male
- Polydactyly in both hands of female
- Polydactyly in only one hand of male
- Polydactyly in only one hand of female
- Polydactyly and brachydactyly
- Brachydactyly

Plate 1

Plate 2

Plate 1.—Photograph of Split Hands of IV-4, Pedigree 1
Plate 2.—Photograph of Split Feet of IV-4, Pedigree 1

The feet of IV-4 are not bilaterally symmetrical, as shown in Plate 2. The central digits of both feet are suppressed with the marginal ones curving inward. On the left foot, the fifth metatarsal bone developed, but phalanges occur only on the fourth and first. A very small portion of the third metatarsal developed, then arched to the right and fused with the first.

The right foot of IV-4 varies slightly from the left in that the phalanges are present on the first and fifth metatarsals, but are absent from the fourth. The second and third metatarsals are missing altogether.

As may be seen from an examination of Pedigree 1, the great grandparents of the propositus were both normal individuals. Among their children, the lobster-claw deformity occurred in one hand and one foot of a son (II-1), while a daughter (II-3) was normal. This son (II-1) married a normal female (II-2), and their two daughters (III-2, III-3) were both phenotypically normal except that III-3 possesses an exceptionally high arch in both feet. She (III-3) married a normal male and gave birth to two sons (IV-4, IV-5), the second (IV-5) being normal and the first (IV-4) being afflicted with the lobster-claw deformity in both hands and both feet (Plates 1 and 2). This affected individual (IV-4) married IV-3, a normal girl, and the couple now has one daughter (V-1) who is afflicted in much the same manner as her father. The other son (IV-5) married a normal woman (IV-6) who gave birth to two sons (V-2, V-3). One of the sons (V-2) is perfectly normal, while the other (V-3) has the second toe missing from each foot. The other daughter (III-2) married a normal male and the couple had two daughters (IV-1, IV-2) who were both normal. Two cousins (III-5, III-6) of III-3 possessed slight deformities of the hands or feet. There were no bones in the little toes of III-5, and in III-6 one hand was slightly smaller than the other. Because of the inability to contact these two cousins, an exact description of their anomalies is impossible.

In referring to Pedigree 1 as a whole we may note that there are three cases of split hands and feet in five generations. The mother of IV-4 from whom information was obtained about generations I and II stated that no evidence of the affliction could be traced prior to its appearance in II-1. The anomaly occurred in both males and females, and approximately half of the offspring of afflicted individuals either showed the trait or were carriers. All afflicted individuals were apparently heterozygous for the condition. One generation, that of III-3 was skipped. These facts suggest that the trait was transmitted as an autosomal dominant gene with incomplete penetrance and varying expressivity.

In figure 2 is shown the pedigree of a family (Pedigree 2) in which only one member, the propositus, is afflicted. The question of whether or not this malformation is hereditary cannot be answered at the present time. The pedigree was included as a part of this paper in order to show the possibility of a mutation having arisen.

The feet of the propositus (III-10, Pedigree 2) are of the typical split foot type. As shown in Plate 3, the central digits are suppressed while the marginal ones curve inward. The clefts, shown in the above mentioned plate, were originally somewhat deeper. The photograph shows the clefts after corrective

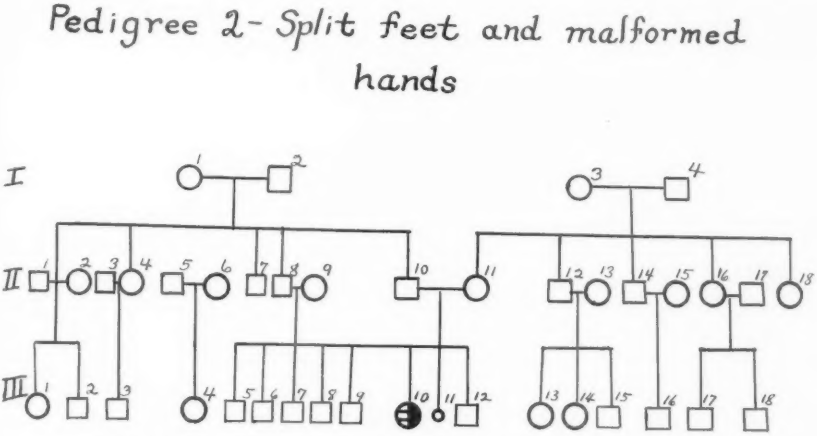

FIG. 2. A three-generation pedigree showing split feet and malformed hands

Plate 3

Plate 4

Plate 3.—Photograph of Split Feet of III-10, Pedigree 2
Plate 4.—Photograph of Malformed Hands of III-10, Pedigree 2

surgery had been performed on each foot in an attempt to close the clefts Each cleft was shortened about one inch. The distal phalanx of the great toe in each foot was broken in order to straighten it as much as possible. The inward arch of these phalanges was originally much greater than the photograph shows them to be at the present time.

The abnormality of the hands of III-10 (Plates 4 and 5) is quite an unusual one. Not only is there a malformation of the bone, but the third and fourth fingers of the right hand are fused. Since this fusion involved only the skin, the affliction was easily corrected by surgical means. The thumbs of the two hands are nothing more than short protuberances. The remainder of the right hand is more completely formed than is the left. With the exception of a short second phalanx, the little finger and the metacarpals of the right hand appear normal. Each of fingers two, three, and four, has but a single element. This

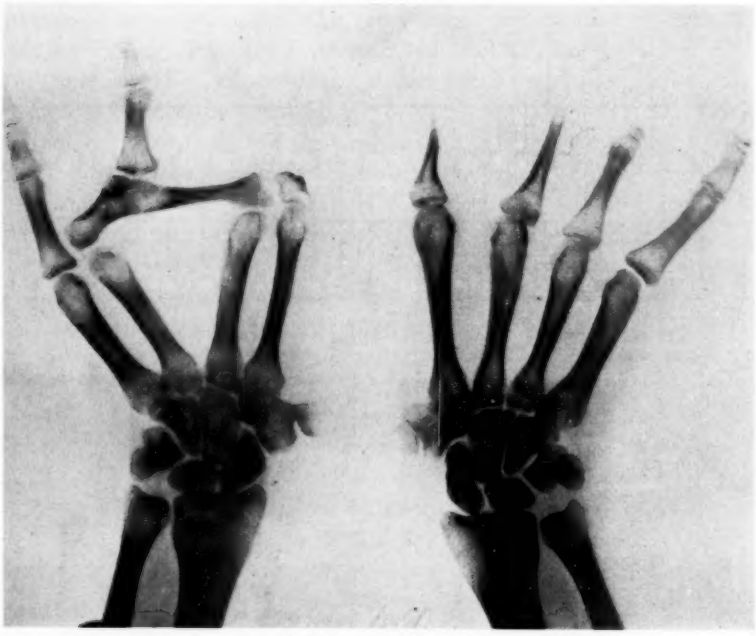

Plate 5.—X-ray of Malformed Hands of III-10, Pedigree 2

element of the fourth finger more nearly resembles the normal phalanx of the fifth finger. However, an examination of the X-ray reveals that although the bases of the first phalanges on the second and third fingers are well formed, the heads taper down to a narrow point. The two terminal phalanges on the second, third, and fourth fingers are absent altogether.

With the exception of a short second phalanx, the fifth phalanges of the left hand of III-10, Pedigree 2, are normal. However, the remainder of the hand is indeed a strange affliction. The first phalanx of the fourth finger developed at an angle of nearly ninety degrees to the normal plane of development, with the distal ends of the third and fourth metacarpals being pushed abnormally

far apart. The apparent reason for this condition is the transverse growth of the first phalanx of the middle finger and its subsequent fusion with the medial side of the head of the first phalanx of the fourth finger. The two terminal phalanges of the fourth finger appear normal. The sole evidence of an index finger is a very small bony structure which appears as if the embryological development was arrested with the formation of the base of the first phalanx.

There is no reason for a detailed discussion of Pedigree 2 since only one individual, the propositus, is affected. A sister (III-11) to the propositus

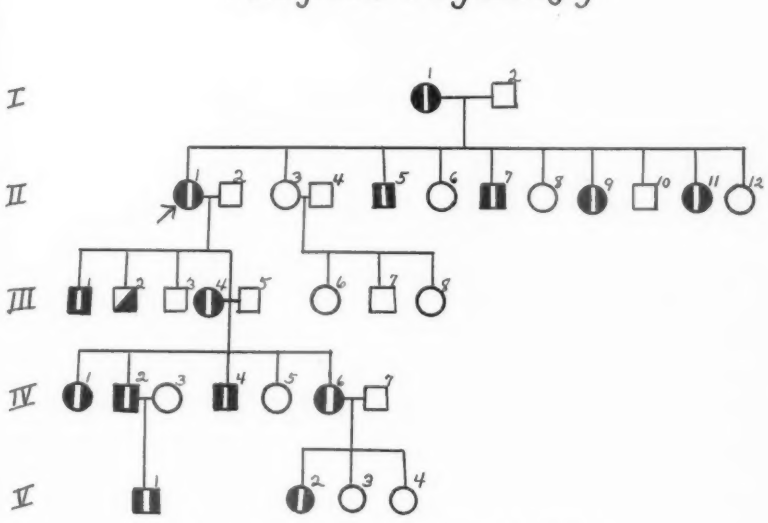

FIG. 3. A five-generation pedigree showing polydactyly

(III-10) was stillborn. However, her hands and feet were normal in every respect. No definite conclusion can be reached at the present time concerning the question of the possibility of this anomaly being hereditary in nature.

Figure 3 shows a five-generation pedigree (Pedigree 3) of a Negro family in which hexadactylism occurs. The extra digits characteristic of this family vary slightly in expression (Plate 6). They occur on both hands in all the afflicted members with the exception of one individual (III-2) on whom the extra finger was found only on the right hand. The extra digits are attached by a fleshy mass on the ulnar sides of the hands near the distal end of the fifth metacarpals. The absence of any bony attachment to the hands as well as any functioning muscles renders the fingers useless and vulnerable to injury.

Consequently, these extra fingers have been amputated from all afflicted individuals with the exception of the propositus (II-1), who retains hers because of superstitious beliefs.

The propositus' hands are shown on Plate 6. She (II-1, Pedigree 3) is eighty years of age. Her mother (I-1) also showed the trait, but her father (I-2) was normal. She had nine brothers and sisters, every other one of whom exhibited the polydactylous trait. One of her normal sisters (II-3) married II-4, a normal man, and all of their three children (III-6, III-7, III-8) were normal. Following the marriage of the propositus (II-1) to a normal man she gave birth to four children. Two of these (III-1, III-4) exhibited the deformity on both hands. One child (III-2) exhibited the trait only on the right hand, and another (III-3) was normal. Of these four children, only III-4 married. Her husband was normal, but of their five children four of them,

Plate 6.—Photograph of Polydactylous Hands of II-1, Pedigree 3

IV-1, IV-2, IV-4, and IV-6, showed the extra digit on both hands; IV-5 was normal. An affected son (IV-2) married a normal woman (IV-3). They had one child (V-1) who was affected. An afflicted daughter (IV-6) married a normal male (IV-7). Of their three children, V-2 possessed the abnormality while V-3 and V-4 were both normal.

Considering the entire pedigree (Pedigree 3) one notes that out of twenty-three members of five affected sibships fourteen exhibited the supernumerary digits. The condition is observed in both sexes, in approximately one-half the offspring from an afflicted parent and in none of the offspring from normal parents. No generation was skipped. From these observed facts, it appears probable that the trait is inherited as a simple Mendelian dominant.

Figure 4 is a six-generation pedigree (Pedigree 4) of a Negro family in which occurs a supernumerary finger-like excrescence known as a "pedunculated postminimi". The extra digit in this particular case takes the form of a fleshy

mass possessing a true fingernail. The attachment to the hand is by a mere pedicle to the lateral margin of the fifth digit in the region of the first phalangeal joint. No supernumerary metacarpal is present. The only affected members of this family, still possessing the extra digits, are V-11 and V-12, ages six years and one year, respectively.

The propositus (IV-4, Pedigree 4) stated that his father (III-1), his grandfather (II-1), and his great-grandfather (I-1) all possessed the postminimus. Three brothers (IV-10, IV-11, and IV-12) and one sister (IV-13) of the

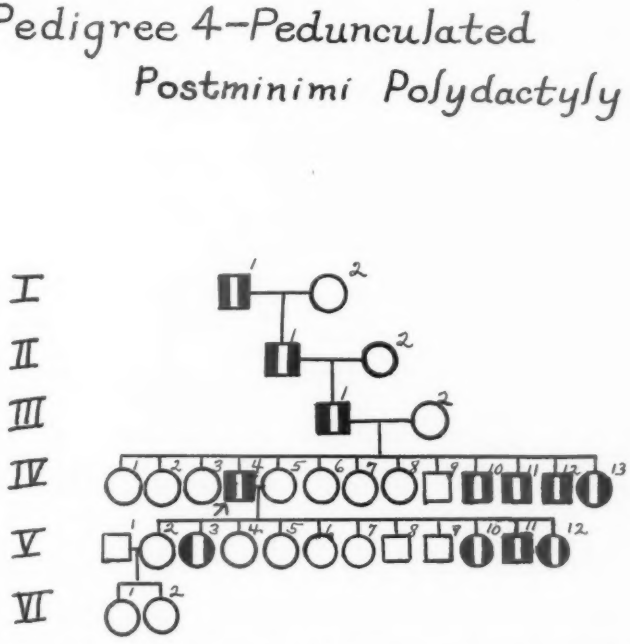

FIG. 4. A six-generation pedigree showing polydactyly (pedunculated postminimi)

propositus were also affected. The propositus stated that only four of his eleven children exhibited the trait (V-3, V-10, V-11, and V-12). A normal child (V-2) married a normal man. They have two normal daughters (VI-1, VI-2). As was concluded for the preceding pedigree, the responsible gene appears to be a simple Mendelian dominant.

Figure 5 is a three generation pedigree (Pedigree 5) in which only one individual is afflicted. The propositus (III-14) was born with six digits on both hands and both feet. The supernumerary digits were amputated three days after birth, with the only remaining visible evidence of their existence being a

small scar on the lateral margin of each appendage. With the exception of the extra toe on the left foot, the attachment of these extra fingers or toes to the hands or feet was by skin. The propositus stated that the left toe had a bony attachment to the foot. Although the surgeon performing the amputation attempted to remove completely this bony structure, a very small portion is still visible on the lateral side of the left foot between the head of the fifth metatarsal and the base of the phalanx.

Another abnormality of the phalanges caused the two distal joints of the fourth and fifth digits on both feet to curve abnormally toward the medial sides of the feet. The propositus was unaware of this condition, and does not know of its occurrence in any other member of her family.

Pedigree 5-Polydactyly and Brachydactyly

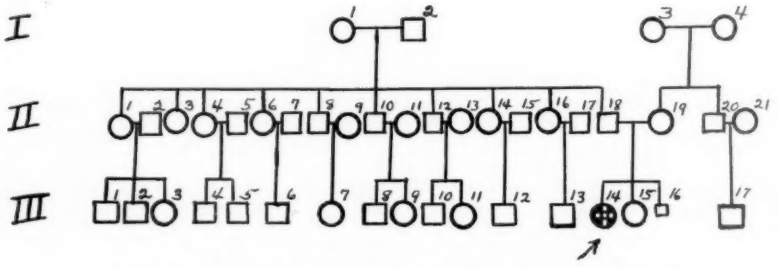

FIG. 5. A three-generation pedigree showing polydactyly and brachydactyly

A third malformation of the hands of the propositus (III-14, Pedigree 5) is a brachydactylous condition in the terminal phalanx of each thumb. This phalanx is shortened and somewhat widened, resulting in a squatty appearance of the whole digit. The nails are about one-half the length of the nails of normal thumbs. These conditions of brachydactyly, polydactyly, and the abnormal inward curve of the fourth and fifth phalanges of the feet occur for the first time in the family history in the propositus.

Since only one individual showed the affliction nothing definite can be said regarding the cause. It may represent a mutation, a recessive phenotype, or an environmentally produced variation. If inherited it would appear probable that the complex of character is the result of a single gene rather than of several genes.

Figure 6 is another pedigree (Pedigree 6) in which only one individual (III-5) is afflicted. However, in this pedigree the anomaly is a brachydactylous condition of the hands (Plates 7 and 8) in which all the digits are affected

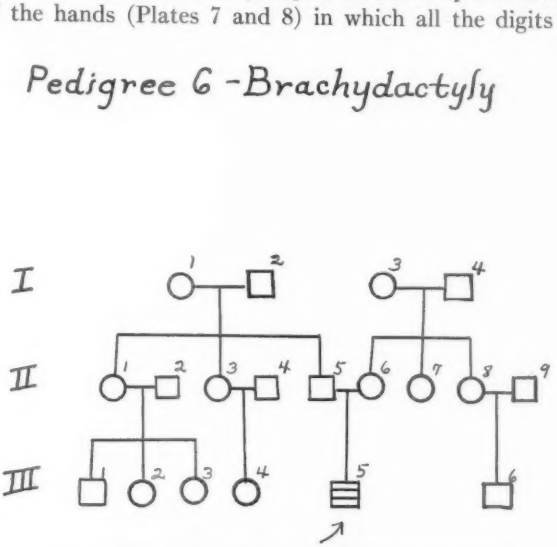

FIG. 6. A three-generation pedigree showing brachydactyly

Plate 7.—Photograph of Brachydactylous Hands of III-5, Pedigree 6

excepting the fourth or ring finger on each hand. The two hands are bilaterally symmetrical, with the exception of the thumbs, the variation in them being that the first phalanx of the right thumb is, although shorter than normal, longer than the corresponding phalanx of the left. Furthermore, the thumb of the right hand is slightly crooked whereas that of the left is relatively

straight. The middle phalanx of the index, the middle, and the fifth finger on each hand is considerably shortened. The first and second phalanges of the index and middle fingers on both hands are shortened, but not to the extent of the middle phalanges. The first phalanx on each thumb is shorter than normal. The fourth fingers on both hands as well as the terminal phalanges of all the digits are completely normal.

Plate 8.—X-ray of Brachydactylous Hand of III-5, Pedigree 6

Since the propositus (III-5) is the only affected individual in Pedigree 6 one may say nothing definite regarding the cause, but it is possible that this brachydactylous case has arisen as a mutation.

SUMMARY AND CONCLUSIONS

Six pedigrees exhibiting anomalies of the hands and feet are presented and discussed. One pedigree shows the split hand and foot, a lobster claw anomaly, occurring in five generations. The anomaly appears to be inherited as an autosomal dominant showing incomplete penetrance, since one generation is skipped, and showing a considerable amount of variation in expressivity. A second pedigree shows a single individual in three generations showing split

feet and malformed hands. Nothing definite may be said regarding inheritance, but it is possible that this single case represents a mutation. A third pedigree consisting of five generations shows polydactyly occurring in fifteen individuals. The condition occurs in approximately one-half the offspring from an afflicted parent and in none of the offspring from normal parents. No generation was skipped. These facts indicate that the condition is inherited as a dominant. A fourth pedigree shows six generations in which twelve members show the pedunculated postminimi type of polydactyly. The anomaly occurs only in the children of an affected parent, while the children of normal parents are normal. Therefore a simple Mendelian dominant appears to be responsible. Pedigree five shows three generations in which only one individual is afflicted. She possessed six digits on both hands and feet which were removed three days after birth, and the terminal phalanx of each thumb shows brachydactyly. Nothing definite may be said about the inheritance. The anomaly may represent a mutation or a recessive phenotype. A sixth pedigree consisting of three generations shows a single individual afflicted with a brachydactylous condition of the middle phalanx of all fingers except the fourth which is normal. It is possible that this condition has arisen as a mutation.

Although these pedigrees may not introduce any new anomaly and show no fundamentally new mode of inheritance, they do show some new variations in expressivity and penetrance and three of them may give evidence of mutations. Thus they do contribute to the total picture of the genetics of hand and foot abnormalities.

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Comments on the Estimation of the Mutation Rate for Achondroplasia[1]

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A RECENT ARTICLE in this Journal by Popham (1953) is devoted to an error made by Mørch (1941) in his indirect estimate of the mutation rate for achondroplasia (chondrodystrophy). This error has been corrected before, namely by Haldane (1948).

I consider that Popham has rendered a useful service in calling Mørch's mistake to more general attention, but I wonder whether the explanation of the error Popham gives is the most straightforward one. If x is the frequency (at birth) of achondroplasia, f the relative fitness of affected, and u the mutation rate, we write $u = \frac{1}{2}(1 - f)x$ to describe the equilibrium condition. One way of looking at this formula is as follows: Suppose there are N normal people in the population, and a number, say A, of them marry achondroplasics. Suppose also that the average normal person, excepting those who marry achondroplasics—whose influence on the general fertility of normals can certainly be ignored—contributes genetically to the production of a children. There will then be $\frac{1}{2}(N - A)a$ children in the next generation (since each parent contributes only half the child's set of chromosomes) from normal by normal matings. Of these $\frac{1}{2}(N - A)a$ children $u(N - A)a$ will be achondroplasics and $(1 - 2u)\frac{1}{2}(N - A)a$ will be normal. There are (near enough) Nx achondroplasics in the population, and they contribute genetically to the production of $Nxaf$ children (as do the A normals who marry achondroplasics). Of these $Nxaf$ children, $\frac{1}{2}Nxaf$ will be achondroplasic and $\frac{1}{2}Nxaf$ will be normal, for we consider the frequency of achondroplasic by achondroplasic matings to be negligible. Thus, in the next generation, the frequency of achondroplasia will be

$$\frac{\frac{1}{2}Nxaf + u(N - A)a}{Nxaf + \frac{1}{2}(N - A)a} = \frac{\frac{1}{2}xf + u\left(1 - \frac{A}{N}\right)}{xf + \frac{1}{2}\left(1 - \frac{A}{N}\right)} = x,$$

the population being in equilibrium.

Now the original formula assumes that the condition is rare, that is, x is small. (Hence we are able to ignore abnormal by abnormal matings, approxi-

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mate the frequency of achondroplasia by Nx, etc.) It also assumes that $f \leq 1$. Moreover, u is small and A/N is bound to be of the same order as x, or smaller. Hence we may approximate the above formulae by

$$\frac{\frac{1}{2}xf + u}{\frac{1}{2}} = x, \qquad \text{so that } u = \tfrac{1}{2}(1 - f)x.$$

Mørch's error did not arise because it is in principle wrong to correct for the fact that only ½ of the children of achondroplasics are themselves achondroplasic. Mørch's error arose because the factor of ½ which f is multiplied by in the expression $\frac{1}{2}(1 - f)$ represents just such a correction, and to correct again, as Mørch did, is redundant.

In his article Popham tells how Mørch used the sibs of achondroplasics as a control group when computing the relative fitness. It is interesting to note that this practice (though in Mørch's case there may have been no choice) is also fallacious. Insofar as fertility is inherited, we might reasonably expect that

1. People with large families will tend to come from large sibships and
2. People with large families will tend to have sibs with large families.

Thus with a sporadic condition (such as achondroplasia is in about ⅘ths of the cases) a large sibship will contribute only one abnormal, who will tend to be comparatively fertile, but it will also contribute, not one, but a large number of very fertile normals. On the other hand, a sibship of, say, two, in which the children will tend to be infertile, will contribute only one infertile normal. Hence the inclusion of two such sibships will bias the comparison of normals and abnormals in such a way as to underestimate the relative fertility of abnormals. One possible way around this difficulty would be to estimate the relative fertility of achondroplasics within each sibship, and then take some sort of average. However, such a procedure requires at the very least the assumption that the relative fertility of affected and normals in sibships of one, which are necessarily excluded, is the same as the relative fertility of affected and normals in sibships greater than one. This assumption may not be justified.

It might also be noted that the marked, exponential maternal age effect which one finds among sporadic cases of achondroplasia, means that achondroplasics tend to come at the end of their sibships (except perhaps when the condition is familial). Hence among contemporary cases the acondroplasics will on the whole be older than their sibs, and therefore parents of larger families than if they and their sibs averaged about the same age. This bias works in exactly the opposite way to the one just described, that is, it tends to result in an overestimate of the relative fertility of achondroplasics. Since, however, we have no a priori reason for believing the two biases to be of the same order, we cannot reasonably hope that they will cancel one another out.

Still another problem in the estimation of the mutation rate for achondro-

plasia derives from the following considerations: Mørch argued that the marked maternal age effect which he observed among his sporadic cases meant that late maternal age (and possibly also paternal age) "caused" the mutation from the normal to the achondroplasic gene. If this is so (though there are perhaps other theories), it follows that the mutation rate which we observe for this condition is not a very satisfactory estimate of the actual mutation rate in the germ plasm. For example, consider two rare dominant conditions, say the conditions A and B, both with the same frequency and relative fitness. Suppose there is a maternal age effect responsible for mutations in condition A and not in condition B. For simplicity, imagine that a mutation to the gene for condition A will occur only in the germ plasm of a woman over the age of 50. Since so few women over the age of 50 have children, the germinal mutation rate in the gametes of women over 50 will have to be higher for condition A than for condition B, in order to maintain both conditions at the same frequency. If, however, the population is in equilibrium with respect to both conditions, their observed mutation rates (by direct or indirect method) will be exactly the same.

In general, if we assume—and I have some unpublished evidence to support this in the case of sporadic achondroplasia—that any paternal age effect observed is due solely to the correlation of paternal age with maternal age, then if N_i is the number of normal children born at maternal age i, $2\Sigma N_i u_i$ of them will be mutants, where u_i is the mutation rate at maternal age i. The mutation rate u' which we actually observe, by Mørch's direct on indirect method, will estimate

$$u = \frac{\Sigma N_i u_i}{\Sigma N_i} = \Sigma p_i u_i \qquad \text{(say)},$$

which is a weighted mean of the individual maternal-age-specific mutation rates. Clearly, some of the individual rates will be greater, and some less, than this average. (For example, among Mørch's sporadic patients, the ratio of the observed number of cases born at maternal age 40 or over to the expected number, based on the multiennial Danish control population which Mørch gives, is 2.4. Using the Rigshospital experience, we find there were 8 sporadic cases of achondroplasia among 94,073 births, giving an incidence at birth of about 8.5×10^{-5}. Hence the mutation rate for women over 40 would be in the neighbourhood of 2×10^{-4}, which is substantially more than the overall rate.) The comparability of averaged rates, with the more straightforward rates encountered in conditions where there is no appreciable maternal age effect, is very dubious.

When suitable data are available, u_i can be evaluated directly from the maternal-age-specific incidence of sporadic cases. By the indirect method, assuming the relative fitness of an achondroplasic does not depend on the

maternal age at which he is born, $u_i = \frac{1}{2}(I_i - xf)$, where I_i is the total incidence of achondroplasia at maternal age i (so that $\Sigma p_i I_i = x$).

There are other difficulties, quite apart from those mentioned above, connected with the estimation of a mutation rate, or of mutation rates, for achondroplasia. All in all, the problem is an extremely intricate one, and I suspect that so far as a general estimate is concerned, we must be content, at least for the present, merely to hope that we have got the order of magnitude right.

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A Preliminary Study of the Population History of the Pima Indians[1]

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THE DISCOVERY THAT a large proportion of the Pima Indians of southern Arizona possess a rare auxiliary cusp (protostylid) on the anterior portion of the buccal surface of the first mandibular molars (Dahlberg, 1950) has made for increased interest in the genetics of the Pima population. The occurrence of this and similar cusps on the second or third mandibular molars is not unusual, but its occurrence on the first molar is extremely rare in modern man. A similar cusp is seen, however, in many of the pre-hominid fossil remains. It has been suggested by Dahlberg (1951) that the appearance of the protostylid in the Pima population is an ativism resulting from the introduction of modifying gene combinations by admixture with other populations. It is thus of interest to assess the relationship of the Pima to other Indian groups in the southwest and to attempt to estimate the extent to which admixture with other populations may have occurred.

The degree of relationship between populations and the amount of admixture between them may be estimated by measurement of the amount of genic exchange between them. The blood group allelic frequencies have been used by many investigators (Boyd, 1939, 1950; Wiener, 1943; Ottensooser, 1944; da Silva, 1948; de Alverez, 1951) as the basis for such estimates for various populations. In the present paper the A-B-O, M-N and Rh allelic frequencies among the Pima Indians are estimated. The A-B-O frequencies of the Pima are compared with those of other Indians of the southwest and of a Caucasoid population to estimate the amount of admixture which may have occurred between various groups during the histories of the present day Indian populations.

BLOOD GROUP FREQUENCIES OF THE PIMA

Blood samples were collected by finger puncture from members of the Pima and Maricopa Indian tribes at Sacaton, Casa Blanca, Salt River and Gila Crossing, Arizona. Several drops of blood were expressed into small tubes which, after labeling, were packed in ice and shipped by air express to Mount Sinai Hospital in Chicago, where serological examination was carried out by

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Dr. I. Davidsohn[2]. All examinations were made within four days after the blood specimens were drawn.

The Pima Indian sample includes eighty-four children of school age and thirteen adults. Most of the adults were selected because of their relationship to children in the sample, for it was hoped that the serological tests would be of value in clarifying familial relationships in the population. Thus the sample is not random, but contains family groups of different size and having different degrees of relationship. Since the same allele may be counted more than once within a family, failure to take into consideration the relationships in a sample may lead to erroneous estimates of the allelic distributions in the population. Cotterman (1947) and Finney (1948a, b) have proposed methods for obtaining efficient estimates of allelic frequencies from family data by weighting each related group according to its degree of relationship. The method proposed by Cotterman is employed in the present paper.

The serological results reported to us by Dr. Davidsohn and arranged according to family size and relationship are given in table 1. If the relationships in the sample are ignored, analysis by the method of Bernstein (1930) gives frequencies as follows:

$Ag^M = .711$	$I^{A_1} = .109$	$R^1\ (CDe) = .574$
$Ag^N = .289$	$I^B = .005$	$R^2\ (cDE) = .337$
	$i = .889$	$R^0\ (cDe)$ or.
		$r\ (cde) = .009$
		$R^z\ (CDE) = .080$
		(by difference)

Although the estimates obtained assuming randomness are consistent estimates of the population frequencies, the standard errors would be smaller than if the relationships were considered, and would indicate greater validity of the estimates than is the case.

The calculation of the M-N allelic frequencies by the method of Cotterman and the values obtained are given in table 2. The phenotypic distribution in each family is given a weight which is related to the coefficient of relationship for each group and the frequency of Ag^N is then calculated using the weighted totals. The scored sample of 97 individuals is equivalent to a random sample of 64.09 individuals.

The calculation of the A-B-O frequencies and the values obtained are given in table 3. For the determination of these frequencies the weight assigned to

[2] We are indebted to Dr. Davidsohn and his assistants at Mount Sinai Hospital for contributing their time and services to the serological examination of the blood samples. Appreciation is also expressed to the many officials, teachers and employees of the Indian Service for their assistance and cooperation in the project.

each family group is a function both of the coefficient of relationship and of the frequency (q) of the recessive allele i, for it is not possible to distinguish homozygous from heterozygous group A and B individuals in the family. Weights

TABLE 1. DISTRIBUTION OF BLOOD TYPES AMONG FAMILIES OF THE PIMA INDIAN SAMPLE

NUMBER OF			NUMBER OF INDIVIDUALS HAVING BLOOD OF TYPE									
Families	Parents	Sibs	M	MN	N	A_1	B	O	Rh_1Rh_2	Rh_2	$Rh_1hr'-$	Rh_1hr+'
1	2	4	3	3	0	0	0	6	4	1	1	0
1	2	3	0	4	1	0	0	5	3	1	1	0
2	2	1	2	3	1	0	0	6	4	0	2	0
1	1	5	4	2	0	4	0	2	2	0	4	0
1	1	2	0	2	1	3	0	0	2	0	1	0
3	0	4	7	4	1	3	0	9	12	0	0	0
2	0	3	5	1	0	3	0	3	1	0	5	0
10	0	2	10	10	0	1	1	18	12	3	5	0
4	Cousins		1	2	1	1	0	3	2	1	1	0
Unrelated			16	11	2	5	0	24	11	5	12	1
Totals			48	42	7	20	1	76	53	11	32	1

TABLE 2. CALCULATION OF THE FREQUENCY OF THE ALLELE Ag^N IN THE PIMA INDIAN POPULATION FROM FAMILY DATA BY THE METHOD OF COTTERMAN (1947)

NUMBER OF PARENTS	NUMBER OF SIBS	NUMBER OF COUSINS	BLOOD TYPE			WEIGHT (W)	W(b + 2c)	2W(a + b + c)
			M (a)	MN (b)	N (c)			
2	4	0	3	3	0	0.3000	0.9000	3.6000
2	3	0	0	4	1	.3571	2.1426	3.5710
2	1	0	2	3	1	.6000	3.0000	7.2000
1	5	0	4	2	0	.2857	0.5714	3.4284
1	2	0	0	2	1	.5000	2.0000	3.0000
0	4	0	7	4	1	.4000	2.4000	9.6000
0	3	0	5	1	0	.5000	0.5000	6.0000
0	2	0	10	10	0	.6667	6.6670	26.6680
0	0	4	1	2	1	.8889	3.5556	7.1112
Unrelated			16	11	2	1.0000	15.0000	58.0000
Totals			48	42	7	—	36.7366	128.1786

$$q_N = \frac{\Sigma W(b + 2c)}{\Sigma 2W(a+b+c)} = .287 \qquad \text{S.D.} = \sqrt{\frac{(p_M)(q_N)}{\Sigma 2W(a + b + c)}} = .040$$

for q values greater and smaller than the estimated population value are assigned to each family group, and the true population frequency of i is obtained by interpolation from the weighted values. The frequencies of I^{A_1} and I^B may

be obtained by applying the same correction factor to determine the proportion of group A and B individuals in the weighted sample. The sample of 97 individuals is, as scored from the determination of the A-B-O frequencies, equivalent to a random sample of 65.25 individuals.

Because of the complexity of the Rh-hr allelic system, it is not possible to obtain frequency estimates by the method of Cotterman unless certain simplify-

TABLE 3. CALCULATION OF THE FREQUENCY OF THE ALLELE *i* IN THE PIMA INDIAN POPULATION FROM FAMILY DATA BY THE METHOD OF COTTERMAN

NUMBER OF PARENTS	NUMBER OF SIBS	NUMBER OF COUSINS	BLOOD GROUP		a + b = k	WEIGHT (W) at q = .85	WEIGHT (W) at q = .90
			A1 or B (a)	O (b)			
2	4*	0	0	2	2	1.0000	1.0000
2	3*	0	0	2	2	1.0000	1.0000
2	1*	0	0	4	4	1.0000	1.0000
1	5	0	4	2	6	.2972	.2931
1	2	0	3	0	3	.5175	.5112
0	4	0	3	9	12	.4100	.4064
0	3	0	3	3	6	.5103	.5067
0	2	0	2	18	20	.6758	.6726
0	0	4	1	3	4	.8970	.8941
Unrelated			5	24	29	1.0000	1.0000
Totals			21	67	88	—	—

At q = .85: ΣWb = 52.6599, ΣWk = 65.4215; ΣWb/ΣWk = .8049
At q = .90: ΣWb = 52.5530, ΣWk = 65.2376; ΣWb/ΣWk = .8056

$$q_i^2 = (.85)^2 + [(.90)^2 - (.85)^2]\frac{.8049 - (.85)^2}{[.8049 - (.85)^2] + [(.90)^2 - .8056]} = .8055$$

$$q_i = .898$$

$$\Sigma Wy = 65.4215 - (.1839)\frac{.8049 - (.85)^2}{[.8049 - (.85)^2] + [(.90)^2 - .8056]} = 65.247$$

$$\text{S. D.} = \sqrt{\frac{1 - q^2}{4\Sigma Wy}} = .027$$

* The blood groups of these children are not included, for their inclusion leads to a less efficient estimate of the population frequency.

ing assumptions may be made. The method may be employed to obtain estimates in the Pima Indian population if it is assumed that the alleles r' (*Cde*), r'' (*cdE*), and r^y (*CdE*) are not found among the Pima. This assumption is justified in part by the fact that these alleles do not appear to have been represented among early (pure) Indians. If the allele r' (*Cde*) is assumed absent in the Pima population the individuals classed serologically as Rh_1 (hr′ −) must have genotype R^1/R^1 (*CDe/CDe*) and the single Rh_1 (hr′ +) individual may

have genotype R^1/R^0 (*CDe/cDe*) or R^1/r (*CDe/cde*). It is not possible on the basis of this sample to distinguish which of these alleles (R^0 or r) may be responsible for the production of the hr′ antigen in this one individual. The symbol R^0 will be used to designate this allele, but the possibility that r is present in the population is not excluded. The single R^0 represented in the sample might be thought to have been introduced into the population at a comparatively recent time, and thus not be widely represented in the population. However the family history of the Rh_1 (hr′ +) individual gives no indication of recent admixture, so that it is probable that this allele is carried by others in

TABLE 4. CALCULATION OF THE FREQUENCY OF THE ALLELE R^1 IN THE PIMA POPULATION FROM FAMILY DATA BY THE METHOD OF COTTERMAN

NUMBER OF PARENTS	NUMBER OF SIBS	NUMBER OF COUSINS	BLOOD TYPE				k	WEIGHT (W) at q = .55	WEIGHT (W) at q = .60
			Rh_1Rh_2 (a)	Rh_2 (b)	Rh_1hr- (c)	Rh_1hr+ (d)			
2	4	0	4	1	1	0	6	0.3570	0.3478
2	3	0	3	1	1	0	5	.4229	.4124
2	1	0	4	0	2	0	6	.6788	.6667
1	5	0	2	0	4	0	6	.3316	.3243
1	2	0	2	0	1	0	3	.5688	.5581
0	4	0	12	0	0	0	12	.4382	.4324
0	3	0	1	0	5	0	6	.5391	.5333
0	2	0	12	3	5	0	20	.7006	.6957
0	0	4	2	1	1	0	4	.9185	.9143
Unrelated			11	5	12	1	29	1.0000	1.0000
Totals			53	11	32	1	97	—	—

At q = .55; ΣWc = 23.1497, ΣWk = 67.2043
At q = .60; ΣWc = 23.0082, ΣWk = 66.7289

$(q_{R^1})^2$ = .3398, q = .583

ΣWy = 66.8553

S. D. = .050

the Indian group. If the allele r'' is not represented among the Pima, those individuals classed serologically as Rh_2 may be of genotypes R^2/R^2 (*cDE/cDE*) or R^2/R^0 (*cDE/cDe*). Since only those individuals classed as Rh_1 (hr′ −) are all homozygotic, only the frequency of the allele R^1 may be determined by the method of Cotterman. The calculation of this frequency is given in table 4. The frequencies of R^2 and R^0 are obtained from the proportions of Rh_2 and Rh_1 (hr′ +) individuals in the weighted sample. The sample of 97 individuals is, as scored for the determination of the Rh frequencies, equivalent to a random sample of 66.86 individuals.

The sum of the estimated frequencies of R^1, R^2 and R^0 is 0.954 rather than

unity. This deviation suggests that there may be additional alleles in the population with a frequency of approximately 0.046. In a sample of 67 individuals an allele having this frequency might not be expressed phenotypically. Such an allele could be expressed phenotypically only as Rh_1Rh_2 in the Pima sample. If the alleles R^1 and R^2 are the only alleles present in the population which produce the phenotype Rh_1Rh_2, then this serological type should comprise approximately 42 per cent of the group, or 28 individuals in the weighted sample. Since 34.04 individuals in the weighted sample are of type Rh_1Rh_2, it is probable that more than one genotype is represented in this group. Only R^1/R^2 (*CDe/cDE*) and genotypes containing R^z (*CDE*) are capable of producing this serological type. If the distribution of types expected assuming R^z present in the population with a frequency of 0.046 is compared with the calculated distribution of the scored sample, a value of $\chi^2_{(2)} = 0.028$ is obtained. This value indicates a probability of greater than 0.8 that the two distributions are the same. The presence of R^z in this Indian group is in agreement with the results of Wiener, Zapeda, Sonn and Polivka (1945), who reported the presence of R^z in Mexican Indians, and of Ottensooser and Pasqualin (1949) who found R^z in Indian populations in Brazil.

The allelic frequencies obtained by analyzing the Pima sample of 97 individuals by the method of Cotterman are as follows:

Ag^N	= .287 ± .040	i	= .898 ± .027	R^1 (*CDe*)	= .583 ± .050
Ag^M	= .713 ± .040	I^{A_1}	= .097 ± .062	R^2 (*cDE*)	= .358 ± .057
		I^B	= .006	R^0 (*cDe*) or	
				r (*cde*)	= .013
				R^z (*CDE*)	= .046

HISTORY OF THE PIMA INDIANS

The histories of the Indians of the southwestern United States, as determined from archeological and ethnological studies, have been reviewed by Wormington (1947). The Pima Indians are believed to be descended from Indians of the Hohokam culture (*Pima: those who have vanished*) who lived in and near the Salt and Gila River valleys from the early part of the Christian era. Other Hohokam groups that lived in the desert region south of the Gila River are believed to have been ancestral to the Papago Indians now living in the same area. The Hohokam peoples are believed to have been descended from groups of the ancient Cochise culture which disappeared from this general region about 500 A.D. (Haury, 1943).

During the late thirteenth century Pueblo groups, probably originally from northern Arizona, moved into the area occupied by the Hohokam peoples. These groups, known as the Salado, remained in the same area as the River Hohokam for some time. Although in some areas the two peoples lived to-

gether in the same 'compounds', both maintained their cultures to a great extent. The Desert Hohokam to the south appear to have had little contact with the Pueblo peoples, for they actively resisted the settlement of their land by the Salado (Haury, 1945). About 1400 A.D. the Salado moved from this area and apparently became dispersed among other populations of the southwest.

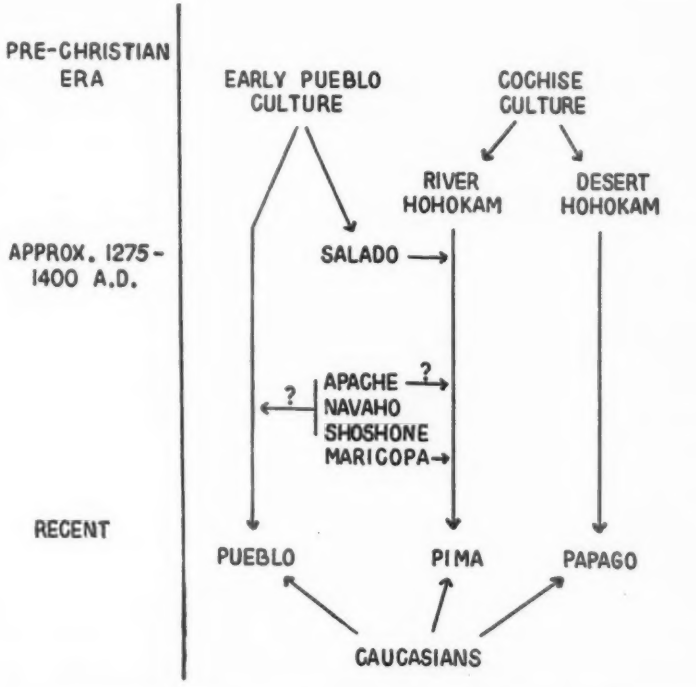

FIG. 1. The historical relationships among Indian populations of Arizona, as based upon archeological studies. Questionable relationships (based upon linguistic similarities and tribal lore) are indicated.

Ethno-archeological studies suggest that the Pima Indians may have a fairly recent biological relationship with the Papago and perhaps with some groups among the Pueblo Indians of the present time, and that the Papago have little or no relationship with the Pueblo Indians. All three Indian groups have probably exchanged genes with Caucasoid groups and with other Indian populations in the southwest. A very general, though incomplete, picture of the history

of these Arizona Indians may be examined to estimate relationships among the populations. The relationships are represented graphically in figure 1.

ADMIXTURE DURING THE HISTORY OF THE PIMA

The proportion of admixture of two populations in producing a third may be easily estimated if the A-B-O blood group frequencies of the three populations are known. To estimate the amount of admixture during the history of the Pima, it is necessary to know the frequencies among the Hohokam and Salado. These frequencies must be estimated from examination of the frequencies among the present day descendents of these tribes. To do this, it is necessary to assume that the Salado tribes were a homogeneous population having the same allelic frequencies as the contemporary population from which the present day Pueblo Indians are descended. It is also necessary, because of limited knowledge of the allelic frequencies among different Indian populations,

TABLE 5. THE A-B-O BLOOD GROUP FREQUENCIES OF INDIAN TRIBES OF THE SOUTHWESTERN UNITED STATES AND OF A REPRESENTATIVE CAUCASOID POPULATION

POPULATION	REPORTED BY	SIZE OF SAMPLE	ALLELIC FREQUENCIES		
			I^A	I^B	i
Papago	Breazeale et al. (1947)	600	.031	0	.969
Pueblo	Boyd (1950)	310	.105	.007	.888
Pima	Present study	65	.097	.005	.898
Spaniards	de Hoyos Sainz (1947)	50,791	.305	.076	.618

to disregard the immigration of other Indians into the Pima, Papago and Pueblo groups.

The A-B-O blood group frequencies among 600 Papago Indians have been reported by Breazeale, Greene and Kantor (1941) and among 310 Pueblo Indians by Boyd (1950). The frequencies in the Pima, Papago and Pueblo Indians and in a Caucasoid population are given in table 5. The Spanish population reported by de Hoyos Sainz (1947) has been chosen because the Caucasoid population of the southwestern United States has been predominantly Spanish until fairly recently. Boyd (1939) has noted that the blood group allelic frequencies of western European populations do not differ strikingly, and that in calculating the amount of admixture of Caucasians with Indian populations, substitution of one European group for another will not materially alter the results obtained. Breazeale et al. and Boyd have not distinguished the subgroups of A in their analyses of the Indian populations. It will be assumed for our purposes that all of the reported group A individuals are of sub-group A_1.

Let U, W and Y represent the percentage contribution of the Caucasoid population to the Pueblo, Pima and Papago Indians respectively, S and Z the contributions of the Hohokam to the Pima and Papago Indians and T and V

the contributions of the Salado to the Pima and Pueblo Indians. Then $Y + Z = 1$, $U + V = 1$ and $W + S + T = 1$. The unknown blood group frequencies of the Hohokam and Salado groups and the percentage contribution of each population to the Pima, Papago and Pueblo populations may be estimated from formulae of the following form:

$$\begin{aligned} W(p_C) + S(p_H) + T(p_S) &= p_P \\ Y(q_C) + Z(q_H) &= q_{Pa} \\ U(r_C) + V(r_S) &= r_{Pu} \end{aligned}$$

p, q and r being respectively the frequencies of the alleles I^{A_1}, I^B and i and the subscript symbols indicating the population in which this frequency is found as follows: C = Caucasoid, H = Hohokam, S = Salado, P = Pima, Pa = Papago and Pu = Pueblo.

Since no group B or AB individuals are found among the Papago, the frequency of these phenotypes in the population is less than 1/600 (.00167). The frequency of I^B among the Papago is then less than .001, which suggests (1) that the proportion of admixture with Caucasians has been low and (2) that I^B may not have been represented among the Hohokam. Since the allele I^B is believed to have been absent among Indians before admixture with other groups (Wiener, 1943; Boyd, 1950) we will assume that I^B did not occur among either the Hohokam or Salado Indians. If this is assumed, then by substitution into the equations the following values are obtained:

$Y \leq .011$	$p_H = .028$	$U = .092$	$p_S = .085$
$Z \geq .989$	$q_H = 0$	$V = .908$	$q_S = 0$
	$r_H = .973$		$r_S = .915$

The Salado and Hohokam frequencies may be substituted into equations for the determination of W, S and T. The value $W = .066$ is obtained either by solution of the equation in q or by the simultaneous solution of the equations in r and p and the equation $W + S + T =$ unity. Substitution of this value of W into the equations in r and p gives values of $S = .042$ and $T = .892$ when the equations are solved simultaneously.

Although these values of W, S and T give consistent results when substituted in the equations for p_P, q_P and r_P, they are not consistent with the hypothesis that the Pima are more closely related to the Papago than to the Pueblo Indians. If the interpretation of the cultural evidence is correct, then we should expect S to be greater than T. If the interpretation is taken to be correct, then the only alternative hypothesis is that other Indian populations, which were not taken into account in this analysis, contributed materially to the genic make-up of the present day Pima and Pueblo populations. Although the identity of these contributors may be suspect, it is not possible, because of lack of

knowledge of their allelic frequencies, to determine the amount of admixture which may have taken place with the Pima and Pueblo populations.

The earliest recorded contact of the Pima with Caucasians occurred in 1530. Thus genic exchange between the two groups may have been taking place over a period of four centuries. The Salado Indians are believed to have dwelt among the Hohokam for a little over 100 years. Thus if there have been no cultural or racial factors affecting the rate of admixture, T should be approximately $W/4$. It may be argued that the proximity of the Salado and Hohokam peoples during the fourteenth century might lead to a greater proportion of admixture between them than between the Pima and Caucasoid populations. It is also possible that social barriers to admixture existed in these extinct groups, for both maintained their ways of life during the period. If it is assumed that $T = .25\ W$ (approximately), it is then possible to estimate the allelic frequencies of the population, or group of populations, which have contributed to the Pima. The values of p and r which are obtained, assuming that the rate of Hohokam-Salado genic exchange was from ½ to 2 times as great as the rate of Pima-Caucasian exchange, are similar, and indicate that the unaccounted-for population has a frequency of I^A greater (greater than .13) and a frequency of i somewhat smaller (less than .87) than the Pima population studied. From 35 to 45 per cent of the allelic distribution in the Pima population may have resulted from admixture with this population, from 47 to 57 per cent may be derived from the Hohokam, approximately 1 to 3 per cent from the Salado, and the remainder, totaling approximately 6 to 7 per cent, from Caucasoid groups.

It is hoped that further study of the blood group frequencies, as well as of other population characteristics, will clarify the relationships among the tribes of this area and make possible conclusions regarding the source of genetically determined traits among the Pima.

SUMMARY

1. A-B-O, M-N and Rh blood group allelic frequencies have been estimated in a sample of 97 Pima Indians from southern Arizona.

2. The frequencies estimated by the method of Cotterman (1947) are as follows:

$Ag^M = .713 \pm .040$	$I^{A_1} = .097 \pm .062$	$R^1\ (CDe) = .583 \pm .050$
$Ag^N = .287 \pm .040$	$I^B = .006$	$R^2\ (cDE) = .358 \pm .057$
	$i = .898 \pm .027$	$R^0\ (cDe)$ or
		$r\ (cde) = .013$
		$R^z\ (CDE) = .046$

3. The population histories of the Indians of the southwestern United States as determined by archeological and ethnological studies, are presented briefly.

The relationship of the Pima to other Indians of the area has been studied by comparing the A-B-O allelic frequencies of these groups to estimate the amounts of admixture occurring during the population histories of the Indians.

4. The allelic distribution of the Papago Indian population is estimated to be derived largely from their assumed Hohokam ancestors (approximately 99 per cent) and in small part by admixture with Caucasoid populations (approximately 1 per cent).

5. Approximately 91 per cent of the distribution among the Pueblo Indian population is derived from extinct Pueblo groups contemporary with the Salado Indians of the early fourteenth century A.D. The remaining 9 per cent of the distribution is the result of admixture with Caucasoid populations.

6. From 47 to 57 per cent of the distribution in the Pima Indian population may be derived from their Hohokam ancestors. Approximately 1 to 3 per cent may be the result of admixture of the Salado Indians with the Hohokam of the Gila and Salt River valleys and approximately 6 to 7 per cent the result of admixture of Caucasoid populations with the Pima. From 35 to 45 per cent of the allelic distribution in the Pima population may have resulted from admixture with another, or other Indian populations of the area having a frequency of I^{A_1} greater and a frequency of i smaller than the present day Pima population. The identity of this group is not known.

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Finger Prints as Criteria of Ethnic Relationship

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INTRODUCTION

DERMATOGLYPHICS provide a tool of unique value for human geneticists and physical anthropologists. The configurations are established long before birth and are not altered by age (except in size), and post-natal environmental circumstances. Permanent and accurate records may be obtained from an individual in a few minutes. Individual records require only a few sheets of paper, and hundreds of such records may be carried in a small traveling bag. Unlike blood samples, dermatoglyphics are not subject to spoilage and may be analyzed years after they are taken. Photographs can be deceptive, as it is often difficult to obtain comparable poses and lighting for a large number of individuals, whereas handprints are free from such disadvantages.

Dermatoglyphics are highly variable, not only from one individual to another, but also from one population to another. These variations are largely heritable, as demonstrated by the fact that monozygotic twins show as great or greater intra-pair than bilateral similarities. In general, the degree of similarity between individuals is correlated with the degree of family relationship. Doubtless multiple genes are responsible for variations in dermatoglyphics and this assumption has likely discouraged many investigators from considering them for research material. Actually such a situation offers several advantages over the employment of well known traits like the various blood groups and other simply inherited variations. A pair of handprints probably provides as much genetic information as do the tests for half a dozen different blood group series. True, we do not know the exact modes of inheritance or the total number of genes involved in dermatoglyphic variations, and perhaps we never shall. But the same may be said of the majority of variations of greatest concern, such as size, intelligence, longevity, disease resistance, and temperament.

Notable advances in livestock and plant breeding have been accomplished through the application of genetic principles, but largely by means of estimates of heritability of quantitative variations rather than through simply inherited one gene variations. Polygenic variations would seem to offer a distinct advantage over simple variations in the area of population genetics, in that they are less subject to the vagrancies of genetic drift. Certainly dermato-

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glyphics are of no importance from the standpoint of assortative mating, which cannot be said to be true of skeletal variations and pigmentation.

Dermatoglyphics are among our most inconspicious variations, and many of the classifications as to types of patterns and configurations are somewhat arbitrary. It requires practice for one to become proficient in analyzing them, yet the rewards would seem to more than justify the time and labor invested. I am not proposing that dermatoglyphics should supplant or are superior to other standard genetic and anthropometric criteria of group relationship. But they have long been neglected, and the time is long overdue when they should take their place alongside the blood groups, pigmentation, hair form, skeletal dimensions, somatotypes, dentition, and other criteria.

INHERITANCE

Data on finger prints far exceed those on other types of dermatoglyphics. Fingerprints vary in type of pattern, angle and size of patterns, and the number of ridges. We shall confine this paper to a discussion of pattern intensity, as expressed both by types of patterns and ridge counts. The two principle types of patterns include whorls and loops. Arches are patternless configurations. Ridge-counts in loops are determined by counting the number of ridges which transverse a straight line from the tri-radius to the pattern core. Whorls have two tri-radii (occasionally three), and ridge-counts include the total number of ridges between each tri-radius and the core. Arches have no ridge-counts.

Extensive investigations of twins and families indicate high heritability of pattern values. In families where both parents have high percentages of whorls, they also occur abundantly among the children, whereas arches are rare. In families where both parents possess high frequencies of arches, arches are frequent among their children and whorls are rare. More variable offspring occur in families where parents have high frequencies of loops, which might be expected, since loops are intermediate in pattern values, as contrasted with arches and whorls at the extremes (Elderton, 1920). Lack of dominance is strongly suggested. Monozygotic twins show greater homolateral than bilateral similarities in pattern types, whereas dizygotic twins manifest approximately two times as many dissimilarities in homolateral comparisons as do monozygotic twins (MacArthur, 1938).

Ridge-count comparisons in the two types of twins also indicate high heritability of pattern values. Geipel (1939) compared the intra-pair differences in ridge-counts in 469 pairs of monozygotic twins with those of 405 pairs of same-sexed dizygotics, and 107 pairs of opposite-sexed dizygotics. The monozygotics showed a mean intra-pair difference of 11.1 ± 0.4 in total ridge-count; whereas the like-sexed dizygotics showed a difference of 39.3 ± 1.4; and unlike-sexed dizygotics a mean difference of 42.3 ± 4.8. Newman (1937)

found intra-pair correlations of +0.46 in 50 pairs of dizygotic twins and of +0.95 in 50 pairs of monozygotic twins, and estimated the heritability of differences in the dizygotic twins to be approximately 90 per cent. These findings present convincing evidence that heredity is the major factor in bringing about individual and group variations in type of pattern and ridge-counts.

As might be expected, ridge-count values show positive correlations with percentages of whorls. The former provides a quantitative criterion, the latter a qualitative criterion of pattern intensity. Accurate ridge-counts require complete and legible prints of all digits, requirements which all too frequently are not fulfilled. Comparatively few data have been compiled pertaining to average total a ridge counts in various ethnic groups. Table 1 shows samples from 9 populations. Note that Egyptians, Northern Sudanese,

TABLE 1. RIDGE COUNT VALUES

POPULATION	NUMBER	MEAN
Northern Sudanese, males	84	193.57 ± 9.61
Egyptian Moslems, males	54	201.61 ± 13.69
Egyptian Copts, males	40	195.37 ± 12.85
American Jews, males	63	185.30 ± 7.93
American Jews, females	50	182.40 ± 11.17
Egyptian females	22	165.86 ± 13.30
Nilotic Negroes, males	79	137.58 ± 7.51
American Protestants, males	50	159.30 ± 7.06
American Protestants, females	50	137.10 ± 8.79

and American Jews show similar values, and that males show higher values than females. Nilotic Negroes and American Protestants, the latter principally of British and northwestern European origin, show considerably lower frequencies than do the peoples of Middle Eastern origin. These trends parallel those observed in the incidence of pattern types, as shown in figure 3.

The most extensive work on the inheritance of ridge-counts was done by Bonnevie. She postulated three independent pairs of alleles, each lacking dominance, as being responsible for the genetic variations. One pair determines the thickness of the epidermis, which in turn regulates the number of ridges. Thickness of epidermis is negatively correlated with ridge count. The genotype is determined by the maximum number of ridges on any of the ten fingers. Bonnevie included only one count in whorls, the one having the highest value. Maximum values of 22 or more indicate genotype *vv*; of from 16 to 21 genotype *Vv*; and those of 15 or less genotype *VV*. Cushioning is postulated as being responsible for wide differences between various fingers of an individual. One pair of alleles (*U* and *u*) determines cushioning for the ulnar side (ring and little fingers) and another pair (*R* and *r*) determines it for the radial side

(thumb, index, and middle fingers). A difference of more than 10 ridges between the maximum count on a hand and one of the ulnar fingers indicates genotype *UU*; of 5–10 ridges genotype *Uu*, of 4 or less genotype *uu*. Corresponding differences between any digit on the radial side and the maximum on the hand are suggestive of genotypes *RR*, *Rr*, and *rr* respectively.

Bonnevie's interpretation agrees closely with family data. It does not agree so well, however, with data from various ethnic groups. This is brought to light by gene frequency analyses. Correctness of a hypothesis to the effect that a single pair of alleles lacking dominance is responsible for observed variations may be easily tested. If the population is in equilibrium the sum of the square roots of the frequencies of the two homozygous phenotypes should not deviate significantly from unity. This test may be employed to

TABLE 2. CALCULATED FREQUENCIES OF GENES *V*, *v*, *R*, *r*, *U*, AND *u* IN FIVE DIFFERENT POPULATIONS. ONLY MALES ARE INCLUDED

NO.	NORTHERN SUDANESE (85)	EGYPTIANS (53)	NILOTES (75)	AMERICAN JEWS (64)	AMERICAN PROTESTANTS (50)
V	.433	.412	.529	.279	.378
v	.563	.713	.346	.661	.648
V + *v*	0.996 ± 0.054	1.125 ± 0.068	0.875 ± 0.058	.941 ± 0.087	1.026 ± 0.070
R	.717	.752	.660	.707	.824
r	.447	.412	.475	.301	.141
R + *r*	1.164 ± 0.054	1.164 ± 0.068	1.135 ± 0.058	1.008 ± 0.087	0.965 ± 0.070
U	.447	.713	.489	.625	.678
u	.553	.474	.565	.414	.489
U + *u*	1.000 ± 0.054	1.187 ± 0.068	1.054 ± 0.058	1.049 ± 0.087	1.167 ± 0.70

particularly good advantage where it is possible to test several populations, differing from each other in frequencies of the traits under consideration. The M and N blood types provide an excellent sample of a trait of this sort. The calculated gene frequencies obtained by this method may also be compared with the actual frequencies. Populations from all over the world have been tested and the calculated frequencies almost always total approximately unity, and agree closely with the actual.

Inspection of table 2 reveals significant deviations from unity in 6 of the 15 gene frequency calculations among the 5 populations. Moreover, comparisons of the frequencies do not always indicate differences in the various populations which are outstanding, both in total ridge counts and in pattern frequencies (See table 3). These observations cast some doubt on the correctness of Bonnevie's hypothesis.

It is of interest to note that with one exception all deviations of significance in table 2 are greater than one. This suggests that Bonnevie may have allowed too small a phenotypic range for the heterozygotes. It should also be re-

TABLE 3. PATTERN INDICES OF VARIOUS POPULATIONS

POPULATION	NUMBER	INDICES			INVESTIGATOR
		♂	♀	♂ + ♀	
Congo Pygmies	101	8.60			Abel
Pygmies	347	9.90			Geipel
	369		9.3		Geipel
	153	10.37			Dankmeijer
	54		10.70		Dankmeijer
Dutch	278		11.36		Dankmeijer
	2,222	11.85			Dankmeijer
Negroes, West Africa	105		11.94		Dankmeijer
	238	12.02			Dankmeijer
Negroes, Spanish Guinea	53		11.40		Pons
	221	12.31			Pons
Spaniards	100		11.89		Pons
	100	12.32			Pons
Russian	11,000		11.89		Semenovsky
	11,000	12.59			Semenovsky
Norwegians	24,518			11.83	Bonnevie
American Catholics (N.W. Eur. & British descent)	122	11.90			Rife
	91		12.04		Rife
American Protestants (British descent)	258		11.91		Rife
	230	12.14			Rife
English	5,000			12.05	Scotland Yard
	2,000	12.03			Waite
Sudan Negroes					
Dinka	132	12.30			Rife
Shilluk	106	12.33			Rife
Bari	72	12.75			Rife
Nuer	110	11.58			Rife
Germans, East Prussia	346		12.18		Duis
	416	12.47			Duis
American Protestants (European descent)	150		12.10		Rife
	154	13.23			Rife
German, Saxony	99,400	12.75			Heindl
Portugese	1,00		12.61		Valadares
	1,000	12.99			Valadares
Ainu	319		12.12		Koya
	213	13.14			Koya
Javanese	1,000		12.94		Dankmeijer
	1,000	13.32			Dankmeijer
Negroes, Sierra Leone	58			13.53	Cummins
Italians	1,579	13.14			Falco
Gypsies, Rumania	187			13.56	Abel
Chilean Indians	246			12.80	Henckel
American Jews	347		13.26		Rife
	144	13.80			Rife
Jews, New Orleans	100		13.95		Cummins & Midlo

TABLE 3. CONTINUED

POPULATION	NUMBER	INDICES			INVESTIGATOR
		♂	♀	♂ + ♀	
	100	13.75			Cummins & Midlo
Jews Germany	1,037	13.87			Kirchmair
Hindu, India	27	13.41			Schlaginhaufen
Hindu, Calcutta	50	14.03			Bisivas
Arabs, Mitwali	138			13.95	Cummins & Shanklin
Egyptians, unselected	1,000	13.70			Rife
	300		13.14		Rife
Egyptians, Coptic, Assint	113	14.03			Rife
Egyptians, Coptic, Cairo	61	14.65			Rife
Egyptians, Moslems, Assint	20	14.60			Rife
Egyptians, Moslems, Cairo	77	14.30			Rife
Northern Sudanese	100	14.22			Rife
Lebanese	1,061	14.30			Shanklin & Cummins
Syrians	1,004	14.55			Leriche
Armenians	179	14.12			Abel
Indians (Mexico & Central America)	633			13.50	Cummins, Cummins Leche & Steggerda
North American Indians (Navaho, Pueblo Arapahoe, Comanche)	400			14.57	Cummins; Downey, Cummins & Goldstein
Ramah Navaho	270			15.39	Spuhler & Bean
Koreans	700			14.46	Kubo
Chinese	300			14.79	Shuno & Mikami
Japanese	12,940			14.90	Kanazawa
Eskimo, Greenland	68			17.40	Abel
Australian Aborigines	89		17.21		Cummins & Setzler
	84	17.73			Cummins & Setzler

membered that each of the populations tested here was of one sex, another possible source of discrepancy, in view of the fact that males possess higher ridge counts than females. She was doubtless correct in assuming that at least one pair of alleles (*Vv*) has a common effect on all digits, and that dominance is lacking.

Most observations seem to indicate that interpopulation trends show similarities in all digits and on both hands. Patterns and ridge counts do not occur at random on the ten digits or on right and left sides. But these interdigital and bilateral variations show essentially similar trends in different populations. Whorls occur more frequently on right fingers, arches on left fingers. Whorls also occur with greatest frequencies on ring fingers and thumbs, arches on index and middle fingers. Moreover, the incidence of arches bears an inverse relationship to the incidence of whorls, although the range of variation is considerably greater in the latter. These trends are well illustrated in figures 1 and 2. While the five populations show great difference in percentages of patterns, the interdigital and bimanual trends are essentially the

same. The greatest interpopulation variation is with respect to the relative percentages of whorls on thumbs and ring fingers. Poll (1938) investigated this phenomenon and pointed out that in some ethnic groups (Negroes, American Indians) the corresponding fingers of right and left hands show greater similarities than do any two fingers of the same hand. This is known as the all pair rule. Caucasians and Mongolians manifest comparable degrees of similarity in the occurrence of whorls on thumbs and ring fingers. The two right and two left digits may show fewer differences than right and left thumbs

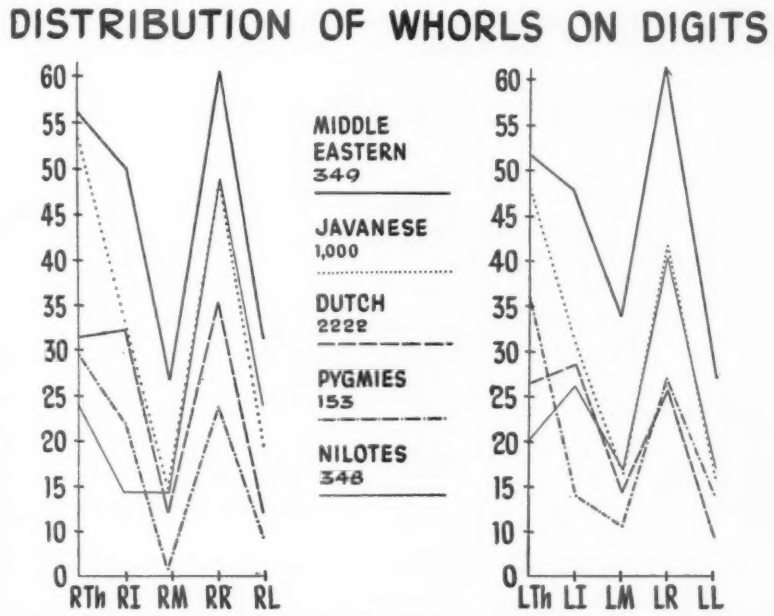

FIG. 1. Percentages of whorls are shown, beginning with the right thumb, followed by index, middle, ring, and little fingers. Data on the Pygmies, Dutch, and Javanese were collected by Dankmeijer (1938). Data on the Middle Easterners include Egyptians, Northern Sudanese, and American Jews; Nilotes include data from Dinka, Shilluk, and Nuer tribes (tables 1 and 3).

and right and left ring fingers. Other fingers still manifest greater bimanual than intra-digital similarity. This is known as the pair group rule.

In figure 1, Middle Easterners, Dutch and Javanese conform to the pair group rule (Dankmeyer, 1938), while Pygmies and Nilotes belong in the all-pair category (Rife, 1953). Nilotes possess more than twice as many whorls on ring fingers as on thumbs, whereas Pygmies have the highest frequencies on thumbs. Javanese and Nilotes show rather striking similarities in percentages of whorls on ulnar fingers, but marked differences on the radial digits. This trend is also apparent in the occurrence of arches.

Dissimilar ulnar and radial trends present the basis for Bonnevie's assumption that a gene (*U*) partially inhibits patterns on the ulnar digits and that another gene (*R*) has a similar inhibiting effect on the radial digits.

Pons (1952) compiled observed gene frequencies (*V*, *v*, *R*, *r*, *U*, *u*) for various populations. Unfortunately, these frequencies do not provide the reader with a very clear picture of the distributions of pattern types and ridge counts in the various populations. Bonnevie may have been correct in postulating three pairs of alleles as being responsible for variations in ridge counts. But the phenotypic criteria do not appear to be very accurate. Her analyses demonstrate the difficulties in making accurate gene frequency estimates for traits whose expression not only depends upon multiple genes, but may also be

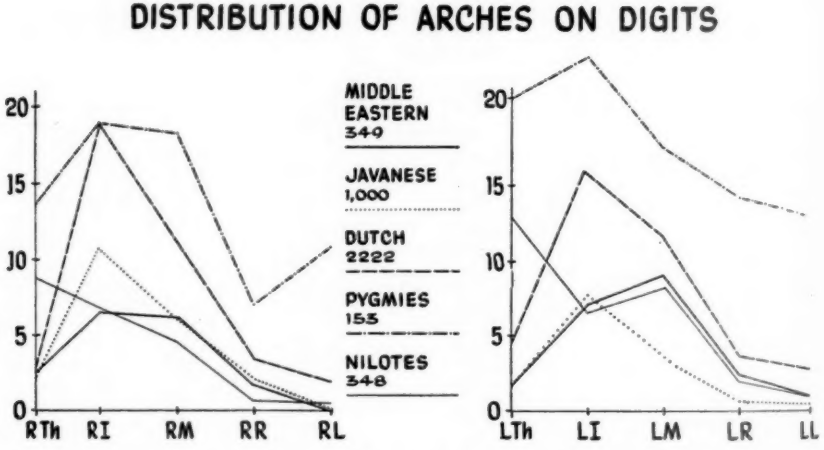

FIG. 2. Data on the percentages of arches among the same populations recorded in figure 1.

modified by non-genetic factors. Fortunately, no dominance seems to be involved, rendering it possible to obtain a more accurate concept of genotypes than if the reverse were true.

GEOGRAPHIC AND ETHNIC DISTRIBUTIONS OF PATTERN INDICES

Data on percentages of whorls, loops, and arches are more abundant than on total ridge counts and gene frequencies. Various indices have been devised for expressing the pattern values as obtained from the percentages of whorls, loops, and arches. Table 3 shows the pattern indices of several populations, and figure 3 illustrates the distribution of pattern values throughout the world. The pattern index is that Cummins, (Cummins and Midlo, 1943) and is obtained by adding twice the number of whorls to the number of loops. An individual having 10 arches has an index of 0, while an individual having 10 whorls has an index of 20.

Inspection of table 3 shows a range of mean pattern values of from 8.+ to 17.+. Most of the populations range between 11 and 15. Australian aborigines have the highest indices of all, African pygmies the lowest of all. It is of interest to note that Australians not only have over 70% whorls, but less than 1% arches; whereas Pygmies have around 20% of both whorls and arches. Bushmen have frequencies corresponding to those pygmies. Thus the two extremes in pattern values are represented by two of the most primitive ethnic groups. Eskimoes also have very high indices. Mongoloid peoples and North American Indians have indices averaging from 14 to 15, followed by Middle Eastern peoples. Some of the indices of Middle Easterners in table 3 exceed 14.25, the value assigned on the map. But these high values are for

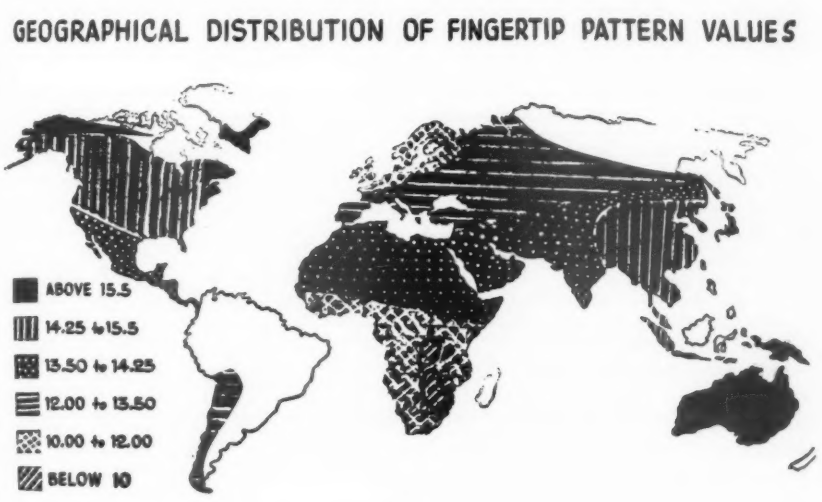

FIG. 3

male populations, who usually have higher pattern frequencies than females. The average is below 14.25. Note that Syrians, Lebanese, Arabs, Egyptians and Jews (both American and German) have essentially similar pattern values. In eastern and southwestern Europe the indices are significantly lower, 12 to 13.50. In Northern Europe and the British Isles values are below 12. The geographical distribution of indices in Europe and Asia is similar to that of blood group antigen B, both increasing from west to east in Europe and Asia, and from north to south in Europe.

Sharp differences between the pattern indices of peoples living in adjacent areas are found in Africa. Arabs, Egyptians, and other Caucasian peoples inhabiting North Africa are characterized by indices averaging around 14, whereas their neighbors to the south have indices averaging close to 12. This is especially noticeable in the Sudan, where the Nilotes in the south have

indices of approximately 12, whereas the northern Sudan of mixed Arab-Negro origin possess indices of over 14. West African Negroes show variable frequencies from one group to another, some well over 12, other considerably below. These fluctuations are too great to be shown on the map, figure 3.

Among American Indians, those in Chile manifest the lowest, and North Americans the highest values. Farther to the north, Eskimoes have even higher indices.

DISCUSSION

Like other criteria of ethnic relationship, pattern indices alone do not give an accurate estimate. The indices of African Negroes are similar to those of west Europeans and British, and those of Semitic peoples do not differ greatly from those of Mongolians. Among Caucasians marked differences are apparent between northwestern Europeans and Semitic peoples. This observation

TABLE 4. ABO BLOOD GROUP DISTRIBUTIONS AND FINGER PATTERN INDICES AMONG EGYPTIANS AND NORTHERN AND SOUTHERN SUDANESE

	NUMBER OF PERSONS	BLOOD GROUPS (%)				NUMBER OF PERSONS	PATTERN INDICES
		O	A	B	AB		
Egyptians	10,045[1]	32.6	35.4	24.3	7.4	1,271	14.25
Northern Sudanese	4,370[2]	45.4	27.8	22.2	4.5	100	14.22
Southern Sudanese	312[3]	52.5	25.6	18.2	4.1	420	12.17

[1] Abdoosh, Y. B. and Salah El-Dewi. 1949.
[2] Corkill, N. L. 1949.
[3] Rife, D. C. 1953.

applies equally well to other criteria. The A, B, O blood groups show marked similarities in their frequencies among Chinese, Negroes and Arabs. Egyptians differ quite significantly from both Arabs and Negroes. It is only when several independent criteria, such as pattern indices, different blood group series, skeletal dimensions, hair form, etc., are employed that one can obtain an accurate estimate of ethnic interrelationships. The problem here is essentially the same as in twin diagnosis or disputed paternity. Similarity between two populations with respect to any single criterion does not necessarily imply they are closely related, whereas a highly significant difference does suggest no close relationship. But marked similarity in many independent criteria certainly indicates close ethnic relationship.

Comparisons of patterns indices and ABO blood group frequencies among Egyptians, northern and southern Sudanese, as shown in table 4, provide an example of the value of independent criteria in evaluating group relationship. Note that northern and southern Sudanese show somewhat similar blood group frequencies whereas they show a great difference in pattern indices. Egyptians show highly different blood group frequencies from those found in both northern and southern Sudanese, yet the pattern indices of northern

Sudanese and Egyptians are strikingly similar. Blood group data alone might lead one to conclude that northern and southern Sudanese are closely related whereas Egyptians are not closely related to either groups of Sudanese. Finger print data alone suggests close relationship of northern Sudanese and Egyptians, but no close relationship between southern Sudanese and either of the other populations. But when both traits are considered it becomes apparent that no very close relationships exist between any of the three populations.

SUMMARY

Dermatoglyphics provide a tool of unique value for human population genetics. More data are available on finger prints than on other types of dermatoglyphics. Pattern indices of finger prints range from approximately 17 among Australian aborigines to below 10 among African pygmies. Mongoloid peoples possess higher pattern frequencies than Caucasians and Negroes. Among Caucasians, Semitic peoples possess the highest pattern indices, northwestern Europeans and English the lowest indices. African Negroes manifest pattern indices similar to western Europeans. American Indians range from 12 in Chileans to over 14 among North Americans.

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BOOK REVIEWS

Précis de Génétique Médicale

By M. Lamy. Paris: G. Doin, 1952, Pp. 256. Broché: 1400 fr. Relié: 1800 fr.

DOCTOR LAMY, Professor of Medical Genetics in the Faculty of Medicine of Paris, is a distinguished pediatrician who is now achieving an equally distinguished position in the field of human genetics. His book, which may be considered the French counterpart of Stern's "Principles of Human Genetics", is obviously written with the needs of the medical student in mind. Theory is presented clearly and with admirable conciseness. The student is spared the cytological details of cell division, for instance, but learns enough of mitosis and meiosis to understand the basis for random segregation.

The first section of the book deals with elementary genetic principles, with many illustrations drawn from clinical material. This is followed by a presentation of the more complicated types of inheritance, and apparent exceptions to the Mendelian patterns. Mutation, penetrance, expressivity and gene-environment interaction are discussed, with due attention to their practical significance in clinical work.

Chapter XIII is a survey of hereditary pathological conditions which, though far from complete (necessarily so, in a volume of this size and type) gives a good idea of the variety and number of human diseases with a genetic etiology. Numerous pedigrees are presented, many drawn from the author's own experience. Chapters on "Medicine and Genetics" and "Genetics and Eugenics" emphasize the difficulties and the opportunities existing in the field of medical genetics. An appendix presents some simple statistical tests useful in the analysis of genetic data.

There are a few minor errors of a typographical nature, which will undoubtedly be corrected in the next edition. The bibliography is representative though not complete, and there is a subject index. This book should prove a creditable addition to the text-books on medical genetics.

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Microscopic Histochemistry, Principles and Practice

By George Gomori, Chicago: The University of Chicago Press, 1952, Pp. 273, $6.00.

Cytochemistry, A Critical Approach

By J. F. Danielli, New York: John Wiley and Sons, 1953, Pp. 139, $4.00.

EVIDENCE for the growing interest in the fields of histo- and cytochemistry is the publication, within the space of a few months, of two books in this country and two abroad[1]. In "Microscopic Histochemistry" Gomori has summarized in a concise and well organized form the results of his extensive studies on the localization of chemical compounds in tissue

[1] Pearse, E., Histochemistry, Theoretical and Applied, London: Churchill, 1953. Lison, L., Histochemie et Cytochemie Animales, Paris: Gauthier-Villars, 1953.

sections. The book is particularly important because, for the great majority of reactions discussed, critical commentary is added from the author's personal experience. Not many workers in the field would be able to do this with any completeness, yet Gomori has ranged so extensively over the broad domain of histochemistry that few important regions have escaped his practical criticism.

Histochemical studies have been of importance to geneticists largely through techniques for the localization of nucleoproteins, particularly when these have been put on a quantitative basis. "Microscopic Histochemistry" discusses the subject of quantitation only in a very brief way, and this is possibly its greatest weakness. The commonly used methods for studying nucleic acids and proteins are discussed, however, with the exception of ultraviolet absorption. Those who would wish a concise discussion, both theoretical and practical, of the Feulgen reaction, for example, or of dye binding by nucleoproteins, will find it here. Undoubtedly the most important section of the book deals with the localization of specific enzymes in tissue sections, a region in which Gomori has been an outstanding authority.

In general "Microscopic Histochemistry" will be a starting point for many workers who wish to employ an unfamiliar histochemical technique in their research. For those already familiar with the methods discussed it will offer many practical suggestions for improvements or simplifications. For those anxious to explore new and untried methods it discusses a number of chemical reactions, as yet unapplied to tissues, that may prove of importance in the future.

The small book by Danielli, "Cytochemistry, A Critical Approach" has quite different aims. Since its contents were originally delivered as a series of lectures at the University of Chicago in 1949, it seems only natural that Danielli should discuss not only the cytochemical and histochemical techniques themselves, but also some problems of biological importance that may be investigated with them. There has been no attempt to cover the field of cytochemistry. Rather, discussion is largely limited to cytochemical reactions for three types of compounds in which the author has been particularly interested, alkaline phosphatase, certain aldehydes, and nucleoproteins. In exercising "the critical approach" Danielli has pointed out in numerous places that cytochemical reactions may lack specificity or may not indicate the precise localization of cellular components because of diffusion artifacts. Many of these criticisms are based on the author's experience and are valuable antidotes to the uncautious conclusions often reached in cytochemical literature. In some places, however, it seems to the reviewer that Danielli continues to be suspicious of well established procedures for no reason except possibly unfamiliarity with the factors involved. For example, in two places he mentions the possibility of nonspecific adsorption of regenerated fuchsin in the Feulgen reaction, a difficulty that Gomori and most other workers feel has been adequately shown to be of little consequence. He is skeptical of the use of all enzymes in the localization of such substances as the nucleic acids, and believes that "final proof can never be found by this type of technique" in spite of the fact that the specificity of these enzymes has been carefully studied by a number of competent investigators who have reached the opposite conclusion. On the other hand, in certain areas Danielli appears to be far too uncritical, particularly concerning the cytological localization of alkaline phosphatase in such structures as nucleoli and the bands of Drosophila salivary chromosomes. It has been demonstrated in several publications during the past two years that the phosphatase reaction cannot be used for such precise cytological localization for the same reason that Danielli mistrusts the Feulgen reaction, namely nonspecific adsorption. Thus although the book is easy to read and contains much useful information, it may be misleading in a number of places to those unfamiliar with Danielli's rather unorthodox

views on certain regions of cytochemistry. Workers already familiar with the field, however, will certainly find the book stimulating.

The fields of histo- and cytochemistry are in need of criticism that will weed out the unworkable reactions from those that can provide us with some information on the chemistry of cells and tissues. Reactions need to be evaluated on the basis of practical experience and with the pragmatic viewpoint: In spite of variables that are bound to occur, can this method still be of importance? In applying this type of criticism, the reviewer feels that Gomori has been far more successful than Danielli.

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Free and Unequal: The Biological Basis of Individual Liberty

By Roger J. Williams (Director, Biochemical Institute, University of Texas) Austin: University of Texas Press, 1953. Pp. xiv + 177. $3.50

A TOO casual reader might regard this book as almost platitudinous in import. We are all aware that in a million faces no two are alike, we know almost in advance that one acquaintance will react in one way and one in another to a given proposition; that people are different few are likely to deny. It is our complacency in the light of this fact and our uncritical estimate of its significance that the author attacks in this volume. If we inquire in what respects and why people are different we are confronted by diverse points of view which in no small degree are responsible for the current division of our world into hostile camps.

The significant differences that exist are real, and they are more numerous, more subtle and more pervasive than the few that first come to mind. The author, a preeminent biochemist with no misgivings as to the importance of vitamines and hormones and with a conviction that proper food is essential even to mental health, emphasizes that he would be among the last to discount the importance of the environment in shaping the human individual. But the very biochemical and nutritional studies which have underscored the significance of environmental factors have also served to force upon him a recognition of the diversity of individual responses and to emphasize striking differences which are innate and all but inescapable. Neither the environment nor the potentialities of the individual can be ignored if our conclusions are to be sound and our studies fruitful.

Many pages are devoted to human differences at various levels. Some of those at a biochemical and others at a purely subjective level are illustrated graphically. Twelve persons were subjected to 31 different biochemical tests and the average for each test was plotted on lines of standard length. When arranged around a point, these lines inscribed a figure which might have been taken as representative of the "average man", but the 12 individual patterns, with some lines reaching scarcely beyond the center and others stretching far out to the side, showed no apparent relation to the average and, except for one pair of twins, very few resemblances to each other. In another series of only 16 subjects as much as a 4-fold difference was found in requirements for thiamin. One acquaintance needs an excess of vitamine A, another an excess of C to maintain normal health and function; neither needs an excess of both. To think of biochemical patterns, or to prescribe vitamines on the basis of averages would be to obscure rather than to make the most of knowledge that is available. In some instances it is almost literally true that "one man's meat is another man's poison". Again and again, and in various ways, the author emphasizes that we must study *men*, not some wholly fictitious "average man".

Differences no less marked were found at the subjective level. Ten workers in a biochemical laboratory, by means of a rather involved elimination procedure, assigned relative weights to 48 selected items which might tend to make life enjoyable. No item was unanimously given first place, and when plotted as before, the average pattern bore little resemblance to that of any one person, and the individuals themselves differed fully as much as did those subjected to biochemical tests. It is evident that no one standardized environment would make all these biochemists happy.

Attention is especially directed to differences in higher mental aptitudes as illustrated by examples which include a number of well-known individuals with transcendent abilities in some respects and mediocre, or even inferior capacities in others. If these abilities could be measured and plotted as were the biochemical traits, the individual patterns—"signatures"—would no doubt be fully as diverse; and the greater the number of items included, the more distinctive and individualized these signatures would become. Whence the differences? Environmental effects are not discounted, but "Every newborn baby has a distinctive and complex pattern of inborn mental capacities. Each item in this pattern is derived from his human forebears, but the pattern with its interactions is unique". This is the basic assumption, but the volume deals not with the processes of heredity but with attitudes toward the products of heredity.

Reducing the problem to its simplest terms, one may ask whether newborn infants are essentially uniform and interchangable, or whether each is a unique and distinctive entity that can not be cast in the mold of any other. The oft-quoted phrase "all men are created free and equal" the author regards, quite rightly it would seem, as an unfortunate paraphrase of an earlier statement in the Virginia Bill of Rights which says that "all men are by nature equally free and independent". There is a difference between being equal and equally free. If all babies were essentially equal, standardized treatment and up-bringing should produce standardized products. This idea seems to be basic, for example, to communistic philosophy, yet every parent with more than one child has its fallacy continually brought home to him. "It is shameful that many children have been alienated from their parents because of the poorly supported supposition that early treatment has been devastating in its effect." While in general paying lip-service to the reality of innate differences, we have become so devoted to the philosophy of the assembly line that we concentrate our attention on averages and means, and are forever trying to fit square pegs in round holes. It is at this point that many of our teachers and others in positions of influence are, without themselves necessarily being aware of it, in almost complete accord with Russian communism. Even UNESCO in a much needed attempt to correct an earlier misapprehension has perhaps tended to create an equally serious new one.

Finally, and this is the main thesis of the book, freedom without differences is meaningless. If we all had the same capacities and interests, and all were equally adaptable, one dietary, one curriculum, one environment and one culture would be the desideratum, with neither the opportunity nor the desire to deviate from an established pattern. From such premises the philosophy of communism flows naturally and more or less inevitably. Almost all of us are in some measure infected by it; but it is precisely because the premises are not sound that we need to save ourselves from their insidious effects by promoting the kind of freedom that will permit each individual to develop according to his own special capacities and realize the potentialities that are peculiarly his in an environment that is conducive to the progress of our western civilization. On such freedom will depend our future happiness and our success in understanding each other and in comprehending and controlling the environmental factors on which we are dependent.

Considerable space is devoted to the implications of this new point of view. The author

finds little ground for considering one man or one race "superior" to another. Men and races may differ in various respects, but they can never be measured along a single linear scale. Recognition of this fact he believes makes for fuller understanding and greater mutual sympathies. No child should be penalized and made unhappy because of his possession, or lack, of special traits or talents. Rather, he should early be made aware of his own strengths and limitations that he may the better direct his efforts. The goals and the world envisioned in latter chapters of the book may seem utopian to some, and no doubt the implementation will be more difficult than would that of a world founded on principles of the assembly line, but the author ventures to hope that "on the basis of careful examination, the uniformity idea with all its connotations will gradually become discredited and discarded and that the ultimate acceptance of the nonuniformity idea will greatly strengthen our love of liberty and foster wholesome human relations."

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BIBLIOGRAPHY OF HUMAN GENETICS

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THIS SECTION is a continued list of references to recent and current articles and books which may be of interest to students of Human Genetics. An attempt has been made and is being made to make the list complete, but to do so is a difficult task. Everyone who finds the list useful and considers a complete one desirable, can be of help by sending to the bibliographic editor, at the address given above, any recent reference which has been missed or any current reference which it seems probably may be missed as the result of its appearance in a journal which is not systematically covered by the bibliographic editor. If a reference to an article is sent in be sure that it is complete with respect to name(s) of author(s), year of publication, title of article, name of journal, volume number, and first and last page numbers. If the reference is to a book be sure that it includes name(s) of author(s), year of publication, title, publisher, place of publication and number of pages.

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